PREOPERATIVE AND INTRAOPERATIVE DIAGNOSIS OF OVARIAN TUMOURS

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Preoperative and intraoperative diagnosis of ovarian tumours
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CONTENTS

General introduction, aims and outline of the thesis

Management of an ovarian tumour is a common problem faced by gynaecologists. The discriminative preoperative evaluation of ovarian tumours is rather difficult, as most ovarian masses are not immediately classifiable. The presumed diagnosis based on preoperative evaluation will guide the decision-making on the surgical approach. On the one hand, an incorrect preoperative diagnosis of benign disease may cause problems in the management of women with unexpected ovarian cancer, because their prognosis is influenced by appropriate surgery by a gynaecologic oncologist. On the other hand, incorrect preoperative diagnosis of malignancy may result in unnecessary anxiety and unnecessary referral to an oncology centre. The studies in this thesis evaluate opportunities to improve the preoperative and intraoperative diagnosis of ovarian tumours.

BENIGN OVARIAN TUMOURS

Most ovarian tumours are benign, especially in women of reproductive age. Many are functional cysts that are harmless and resolve spontaneously. An ovarian cyst is a (mostly) fluid-filled sac that forms in the ovary. Ovarian cysts vary in size and may occur at different sites in the ovary: the most common type develops when an egg-producing follicle does not rupture and release the egg, but instead swells with fluid and forms a follicular cyst. Other types of benign cysts are dermoid cysts, cystadenomas and endometriomas. Benign ovarian tumours are usually slow-growing. Although benign ovarian tumours can probably be safely left in situ, treatment is often surgical.

BORDERLINE OVARIAN TUMOURS

Borderline ovarian tumours, or ovarian cancers of low malignant potential, are classified between benign and malignant tumours as distinct entities. They differ from ovarian cancers by the absence of stromal invasion. They make up 15% to 20% of all epithelial ovarian tumours. Borderline ovarian tumours are primarily diagnosed in young women, are often found at an early stage, and have a high overall 5-year survival rate of up to 95%.[1] Standard surgical treatment is staging surgery, which includes bilateral salpingo-oophorectomy and peritoneal staging procedures without lymph node sampling. In young women with early stage borderline ovarian tumours fertility-preserving staging, leaving the uterus and at least a part of one ovary in situ, is sufficient.

MALIGNANT OVARIAN TUMOURS

Ovarian cancer is the fourth most common cause of cancer-related death in women and has the worst prognosis of all gynaecological cancers. According to the data of the Dutch Association of Comprehensive Cancer Centres (ACCC), in the Netherlands in 2013, ovarian cancer was diagnosed in 1259 women, and 1010 women died from this disease.[2] The majority of the malignant ovarian tumours are epithelial ovarian cancers, accounting for more than 90% of all ovarian malignancies. Epithelial ovarian cancers are subdivided in serous, mucinous, endometrioid, clear cell, and undifferentiated adenocarcinomas.[3]

Ovarian cancer confined to the ovary (International Federation of Gynecology and Obstetrics [FIGO] stage I disease) has a 5-year survival of 92%.[4] However, detection of ovarian cancer at an early stage is difficult as ovarian cancer mostly remains asymptomatic in the earlier stages. Furthermore, the identity of a precursor lesion and how it develops into ovarian cancer is still not clear. No screening method has yet been proven to significantly affect mortality, even in a high-risk population.[5] Consequently, approximately 70% of the patients is diagnosed at an advanced stage of disease (FIGO IIB-IV). At that stage, the 'silent lady killer' has already spread throughout the abdomen and 5-year survival rates are poor.[4]

The treatment of women with ovarian cancer depends on the stage of the disease. Optimal staging is necessary to determine which patients need adjuvant treatment, as only low-risk patients are treated with just surgery. According to the Dutch ACCC, optimal staging means: inspection and palpation of all serous surfaces in the abdominal cavity; aspiration of ascites or peritoneal washings for cytology; hysterectomy with bilateral salpingo-oophorectomy; infracolic omentectomy, and biopsies of: all locations to which the ovarian tumour has adhered to or grown into; all macroscopic locations and adhesions that are suspect; peritoneum of the pouch of Douglas; bladder peritoneum; peritoneum of the pelvic walls; left and right paracolic gutters; and the right diaphragm. Lymph node sampling should consist of resection of at least ten nodes, with lymph nodes sampled from the paraaortic and paracaval region, around the common, internal and external iliac vessels on both sides and from the obturator fossa. In case of a sub-optimal surgical staging, or in case of a poorly differentiated tumour, women with early stage ovarian cancer may benefit from adjuvant chemotherapy.[6]

Treatment of women with advanced stage ovarian cancer consists of maximum cytoreductive surgery and platinum-based chemotherapy. The goal of primary cytoreductive surgery is to resect all macroscopic tumours and involves removal of the adnexa, uterus, and the infracolic part of the omentum. The amount of residual disease after primary cytoreductive surgery is an important predictor of prognosis.[7,8] Ovarian cancer surgery is not part of the training programme of general gynaecologists. Studies have shown that survival rates of ovarian cancer patients are better when surgery is performed by a gynaecologic oncologist compared to surgery performed by general gynaecologists, leading to a 5- to 8-month median survival benefit for patients with

advanced stage disease. Furthermore, it has been shown that better debulking surgery results were obtained in high volume institutions.[9-17]

SPECIALISED CARE

In the Netherlands, the treatment of ovarian cancer was formally centralised from January 2013 on. Before that, centralisation was already starting to develop. Different types of hospitals worked together within the framework of the eight comprehensive multi-hospital cancer centres. In the region of Nijmegen, the Radboud university medical center officially formed a regional collaboration with ten hospitals in the east of the Netherlands in the year 2000. The main goal of this collaboration was the improvement of care for gynaecological oncological patients, especially ovarian cancer patients. As part of this collaboration, gynaecologic oncologists at the centre hospital regularly assisted the gynaecologists in the community hospitals when performing surgery on patients with suspected ovarian cancer. The decision on when to operate in cooperation with a gynaecologic oncologist was difficult, despite improvements of imaging techniques and available tumour markers. A retrospective cohort study on all ovarian cancer patients in the Netherlands newly diagnosed between 1996 and 2003 showed that the majority of the ovarian cancer patients did not receive care in specialised settings.[14,18] On the other hand, since the preoperative assessment of an adnexal mass is difficult, it was too often the case that gynaecologic oncologists were involved in surgery for benign ovarian cysts.

PREOPERATIVE EVALUATION OF OVARIAN TUMOURS

Symptoms and physical examination

Most benign ovarian cysts do not cause symptoms. If present, the symptoms of benign ovarian cysts can include: mild abdominal pain; bloating or a feeling of fullness or pressure; dyspareunia; menstrual irregularities; sudden, sharp abdominal pain, fever and nausea in case of a torsion or rupture.

Borderline tumours and ovarian cancer in an early stage are usually asymptomatic as well. Physical findings are diverse and include the signs and symptoms that are also commonly caused by benign diseases. When these symptoms are caused by ovarian cancer, they tend to be persistent and represent a change from normal. Other symptoms of ovarian cancer can include: fatigue; indigestion; back pain; and constipation. However, these symptoms are aspecific and are also caused by other conditions, and occur just about as often in women who do not have ovarian cancer.[19] When an ovarian mass is presented with ascites it is highly predictive of a borderline tumour or ovarian cancer. On the other hand, nearly half of borderline tumours and approximately 80% of early stage ovarian cancers do not produce ascites.[20]

Imaging

If an ovarian tumour is suspected based on the patient history and physical examination, transvaginal ultrasonography (TVS) is the most commonly employed imaging modality to further assess the pelvis. TVS allows for detailed imaging of the ovaries, determining their size and aspect, and the detection of morphological changes that may signify a malignancy. Ultrasonographic characteristics of malignancy are: multilocularity; septum thickness of more than 3 mm (no sharp boundary line); echo-dense areas; papillary masses in the cyst cavity; and ascites. Ultrasound images representative of benign and malignant pelvic tumours are shown in Figure 1.

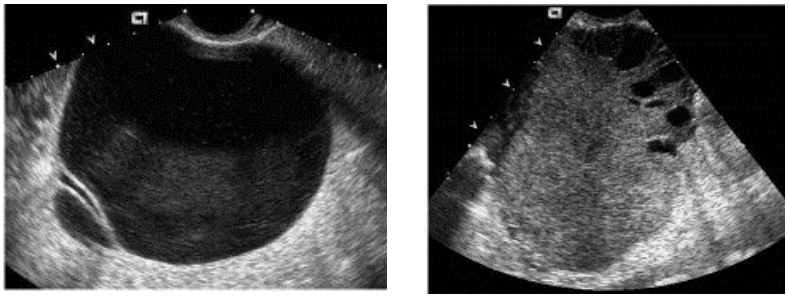

Figure 1. (A) Benign tumour characterised by absence of solid components and absence of irregularities. (B) Malignant tumour characterised by presence of solid components and presence of irregularities.[21]

Experienced ultrasonographers in most cases are able to differentiate malignant from benign masses. The accuracy and the level of interobserver agreement both correlate with experience.[22] TVS is more sensitive than computed tomography (CT) scanning for the detection, assessment, and characterisation of pelvic masses.[23,24] CT scan findings of complex functional cysts, benign ovarian tumours, and inflammatory and/or infectious masses can mimic ovarian malignancies. Magnetic resonance imaging (MRI) can also be used in the setting of a sonographically indeterminate adnexal mass. The presence of fat, haemorrhage, mucin, fluid, and solid tissue within an ovarian mass can be determined with the aid of MRI and is most useful in determining whether a mass is most likely benign.[25]

A relatively new diagnostic tool in the assessment of an ovarian tumour is three-dimensional (3D) ultrasound. This technique visualizes the ovarian mass in all three planes (longitudinal, transverse and coronal), which offers the possibility of volume measurements and quantification of echogenicity of the ovarian tumour. A multicentre prospective study by Geomini et al.[26] showed that the use of 3D ultrasound significantly improved the prediction of malignancy as compared to patient characteristics and 2D ultrasonography (areas under the receiver operator characteristic curve of 0.92 and 0.82, respectively, p=0.02), although the study included a relatively small sample size. Large prospective multicentre studies are needed to establish whether the improvement in diagnostic accuracy of the adnexal mass by the addition of 3D ultrasound is clinically relevant, especially since 3D ultrasound is currently not a standard tool in daily clinical practice.

Several authors[27-30] have proposed the use of colour Doppler in those ovarian lesions that are difficult to classify, exhibit a complex appearance, or are suspicious for malignancy. The true diagnostic accuracy of this approach still needs to be determined.

Tumour markers

The serum tumour marker cancer antigen 125 (CA 125) level is widely used as a marker for a possible ovarian cancer in the primary assessment of an adnexal mass. In 80% of women with ovarian cancer, the CA 125 in serum is raised. This applies to a lesser degree to mucinous tumours and early stage disease. In women with early stage ovarian cancer, the CA 125 value in serum is only raised in 45% of the cases. CA 125 is not specific for ovarian cancer and may be elevated in a number of other malignancies, but also in benign ovarian tumours, menstruation, endometriosis, pregnancy, and pelvic inflammatory disease.[31] It is therefore necessary to combine CA 125 with new tumour markers that provide better diagnostic efficiency. Recently, human epididymis protein 4 (HE4) has been proposed as a tumour marker for ovarian cancer.[32,33] Studies suggest that HE4 sensitivity and specificity in gynaecological diseases are better than with CA 125 and that both tumour markers are complementary. Moore et al.[33] showed in their study that the combination of CA 125 and HE4 added 33.1% to the sensitivity of only CA 125 and 3.5% to the sensitivity of only HE4. It needs to be further validated in order to decide if it should be recommended as a parameter for daily clinical decisions on patients with an ovarian mass.

Besides conventional biomarkers, proteomic techniques offer a promising area of investigation. It regards cancer as a genetic disease, with genetic alterations leading to the production of abnormal proteins. Proteomic technology aids in the characterisation and validation of dysfunctional or altered proteins.[34] An advantage is the ability to identify new potential biomarkers present in small amounts in the serum. Due to recent technologic advances in proteomics and also genomics, there have emerged many individual biomarkers that are currently being investigated for use.[35,36]

Prediction models

In spite of careful interpretations, the diagnostic procedures do not allow for establishing a definitive diagnosis of ovarian cancer preoperatively, but will only suggest its presence. Several efforts have been made to develop a practical and cost-effective method for the ovarian cancer risk estimation in patients with an adnexal mass. Table 1 presents an overview of externally validated prediction models.

Table 1. Externally validated diagnostic models to estimate the risk of malignancy in adnexal masses.

Model	Type of model	Variables	Cut-off level
RMI-1 (Jacobs et al., 1990)	Scoring system	(i) menopausal status, (ii) CA125, (iii) multilocular cysts, (iv) solid areas, (v) metastases, (vi) ascites, and (vii) bilaterality	200
RMI-2 (Tingulstad et al., 1996)	Scoring system	same as RMI-1	200
RMI-3 (Tingulstad et al., 1999)	Scoring system	same as RMI-1	200
RMI-4 (Yamamoto et al., 2009)	Scoring system	same as RMI-1, with the addition of (vii) largest diameter of lesion	450
Tailor et al., 1997	Logistic regression	(i) papillations, (ii) age, and (iii) time averaged maximum velocity in tumour vessels	50%
Prömpeler et al., 1997	Logistic regression	(i) ascites, (ii) solid lesion without shadowing, (iii) cyst with >30% solid part, (iv) diameter of the lesion, (v) multilocularity, and (vi) surface of the cyst	10%
Timmerman et al., 1999	Logistic regression	(i) colour score, (ii) CA125, (iii) papillations, and (iv) menopausal status	25%
Timmerman et al., 1999	Logistic regression	(i) papillations, (ii) irregular internal cyst wall, (iii) unilocular cyst, (iv) ascites, (v) bilaterality, (vi) menopausal status, and (vii) CA125	60%
Jokubkiene et al., 2007	Logistic regression	(i) size of lesion (mean of 3 diameters), (ii) size of largest solid component (mean of 3 diameters), and (iii) any irregularity	12%
LR1 (Timmerman et al., 2005)	Logistic regression	(i) personal history of ovarian cancer, (ii) previous use of hormonal therapy, (iii) age, (iv) maximal diameter of the lesion, (v) pain, (vi) ascites, (vii) blood flow within papillary projection, (viii) solid tumour, (ix) maximal diameter of the largest solid component (bounded at 50 mm), (x) irregular internal cyst walls, (xi) acoustic shadows, and (xii) colour score of intratumoral blood flow	10%
LR2 (Timmerman et al., 2005)	Logistic regression	(i) age, (ii) ascites, (iii) blood flow within a solid papillary projection, (iv) maximal diameter of the largest solid component (bounded at 50 mm), (v) irregular internal cyst walls, and (vi) acoustic shadows	10%
Sassone et al., 1991	Morphologic score	(i) inner wall structure, (ii) wall thickness, (iii) septa, and (iv) echogenicity	9
Depriest et al., 1993	Morphologic score	(i) tumour volume, (ii) wall structure, and (iii) septal structure	5
Lerner et al., 1994	Morphologic score	(i) wall structure, (ii) acoustic shadows, (iii) septa, and (iv) echogenicity	3

Table 1. Continued

Model	Type of model	Variables	Cut-off level
Ferrazzi et al., 1997	Morphologic score	(i) wall structure, (ii) septa, (iii) vegetation, and (iv) echogenicity	9
ANN1 (Timmerman et al., 1999)	Artificial neural network	(i) papillations, (ii) colour score, (iii) menopausal status, and (iv) CA125	45%
ANN2 (Timmerman et al., 1999)	Artificial neural network	(i) papillations, (ii) smooth surface, (iii) unilocularity, (iv) ascites, (v) bilaterality, (vi) menopausal status, and (vii) CA125	60%
Simple Rules (Timmerman et al., 2008)	Ultrasound rules	malignant criteria: irregular solid mass, colour score 4, irregular multilocular-solid mass ≥100 mm, ascites, at least 4 papillary structures; benign criteria: unilocular cyst, colour score 1, smooth multilocular tumour with largest diameter <100 mm, presence of acoustic shadows, presence of solid components where the largest solid component has a largest diameter <7 mm	n/a
ROMA (Moore et al., 2009)	Biomarker algorithm	(i) CA125, (ii) HE4, and (iii) menopausal status	n/a
OVA-1 (Ueland et al., 2011)	Biomarker algorithm	(i) CA125, (ii) transferrin, (iii) transthyretin (prealbumin), (iv) apolipoprotein A1, and (vii) beta-2-microglobulin	n/a

n/a, not applicable.

The Risk of Malignancy Index (RMI), introduced by Jacobs et al. in 1990,[37] was the first prediction model suitable for use in clinical practice, and defines the optimal combination of diagnostic criteria. The RMI is the product of the ultrasound score (*U*), the menopausal score (*M*), and the absolute value of serum CA 125 level:

RMI = *U* x *M* x CA 125

The model for the original RMI was provided by a stepwise logistic regression analysis, which revealed that menopausal status, ultrasound score and serum CA 125 level were all significantly ($p<.01$) and independently related to the likelihood ratio for malignancy. The contribution of CA 125 to the RMI was critical for assigning masses to the malignant category, whereas the main contribution of ultrasound was identifying benign disease. Menopausal status was, but age was not significantly related to the likelihood ratio, nor was any other interaction term significant. The exact formula for the likelihood ratio found was simplified in order to create the RMI, without loss of diagnostic precision. The likelihood ratio and logistic regression analysis were independent of the ratio of benign to malignant lesions in the studied population. The RMI can therefore be generalised to predict risk of malignancy in various populations.

Five ultrasound features suggestive of malignancy make up the ultrasound score. These include the presence of multilocular lesions, solid areas, bilaterality, ascites, and intra-abdominal metastases. A *U* of zero was given when none of these features were present, a *U* of one was given if one of these features was detected, and a *U* of three was given if two or more of these features were detected. Premenopausal women were given an *M* of one and postmenopausal women were given an *M* of three. In cases with no ultrasound features suggestive of malignancy, the RMI becomes zero irrespective of the value of serum CA 125 level.

In 1996, Tingulstad et al.[38] created their own model of RMI (RMI-2) by performing a stepwise forward logistic regression to re-establish independent predictors of malignancy. The best discrimination was found between the ultrasound score of two or more versus one or zero. Therefore, in the final model of RMI-2 the ultrasound variable was dichotomised into a comparison of ultrasound score zero or one as reference group (*U*=1) compared with that of two or more features (*U*=4). Similarly, an *M* of one was given to premenopausal women and an *M* of four to postmenopausal women. The main consequence of this modification of the RMI is that in cases with no ultrasound features suggestive of malignancy, the RMI could be over 200 in the presence of an elevated CA 125 level. Tingulstad et al. modified the RMI again in 1999 (RMI-3)[39] by combining the ultrasound score of zero or one to give *U*=1, whereas for two or more features, *U*=3 was used in the equation. Also, *M* was given a value of one when premenopausal, and three when postmenopausal.

The three versions of the RMI have been validated retrospectively and prospectively in various clinical studies[37-50] where a cut-off value of 200 showed the best discrimination between benign and malignant adnexal masses, with high sensitivity and specificity levels (sensitivity 51–90%, specificity 51–97%). A fourth RMI was introduced by Yamamoto et al. in 2009,[51] which included tumour size as an additional parameter. The RMI is very popular because of its simplicity: little experience is needed to detect the ultrasound features that have to be scored.

After the introduction of the tumour marker HE4, the Risk of Ovarian Malignancy Algorithm (ROMA) was developed, which is an algorithm that uses both CA 125 and HE4 along with menopausal status in a logistic regression model to classify patients with a pelvic mass into high-risk or low-risk groups for having epithelial ovarian cancer.[52-55] The main advantage of the ROMA algorithm is the sensitivity for the prediction of ovarian cancer in women with an ovarian tumour. A disadvantage of the ROMA is its relatively complex calculation method. More studies are necessary to clarify the best cut-off values for ROMA and to judge the validity of this instrument before its application in clinical practice.

The International Ovarian Tumour Analysis (IOTA) models and rules (LR2 and Simple Rules) characterise adnexal tumours based upon the presence or absence of typical ultrasound features of malignancy (e.g. ascites, increased vascularisation, solid components, tumour size, papillary projections and irregular cyst walls).[56,57] The most recent systematic review and meta-analysis evaluating the performance of prediction models and rules to characterise adnexal pathology

concluded that both LR2 and the Simple Rules perform better in differentiating the benign or malignant nature of an adnexal mass in a preoperative setting than any other included model.[58]

More recently, the IOTA group developed a new multiclass prediction model to preoperatively discriminate between benign, borderline, stage I invasive, stage II-IV invasive, and secondary metastatic ovarian tumours: the Assessment of Different Neoplasias in the adneXa (ADNEX) model.[59] This model uses three clinical predictors (age, serum CA 125 level, type of centre) and six ultrasound predictors (maximal diameter of lesion, proportion of solid tissue, more than 10 cyst locules, number of papillary projections, acoustic shadows, and ascites). The first evaluation of the ADNEX model in an international multicentre prospective cohort study showed promising results.

To this day, no single prediction model has gained universal acceptance in routine daily practice. Ultimately, the optimal approach to characterizing ovarian masses remains the subjective interpretation of the ultrasound features of a mass by an experienced ultrasound examiner.[22,60,61]

INTRAOPERATIVE EVALUATION OF OVARIAN TUMOURS

An additional diagnostic procedure for the assessment of an adnexal mass is frozen section analysis during surgery. Frozen section analysis is widely used in the intraoperative evaluation of ovarian tumours and is generally accepted as a reliable method.[62-64] It helps in making an informed decision on the extent of surgery, such as removal of the contralateral ovary, hysterectomy, or the necessity for staging, and therefore preventing both under- and overtreatment. The frozen section procedure includes the examination of one or two sections of the most suspicious parts of the removed tissue. The diagnosis may be expected within 20-30 minutes and is preferably limited to a "benign", "borderline" or "malignant" diagnosis. The technical quality of the frozen section is lower compared to the formalin fixed, wax embedded tissue processing.

The accuracy in diagnosing ovarian cancer has been assessed in previous studies. A systematic review by Geomini et al.[62] showed high levels of sensitivity and specificity (71–100% and 98–100%, respectively) for frozen section analysis. In contrast, frozen section analysis of borderline ovarian tumours appears to be less accurate. Tempfer et al.[65] presented a pooled analysis of four studies that included 317 women with borderline ovarian tumours. The overall sensitivity was 71% and the positive predictive value was 84%.

As a frozen section procedure only includes the examination of one or two sections of the most suspicious parts of the removed tissue in a limited time frame, frozen section analysis cannot be accurate in all cases. The comparison of all kind of tumours has shown that most misdiagnoses on frozen sections occur in mucinous ovarian tumours.[62,64,66,67] Since mucinous ovarian tumours frequently contain benign, borderline, and malignant components at the same time and have

relatively larger dimensions, they are more likely to be underdiagnosed than serous tumours.[68] The most common problems in differential diagnosis include the distinction of borderline tumours from carcinomas, and the distinction of primary versus metastatic carcinoma.

A report by Geomini et al.[69] has shown that also tumour size has an effect on the accuracy of frozen section analysis. In masses with a diameter of 10 cm or larger, a benign result of the frozen section analysis was less reliable than in masses with a diameter of less than 10 cm. In women with masses of 10 cm or larger, 11% of the women in whom frozen section analysis indicated a benign cyst turned out to have a malignant or borderline tumour according to the final pathology. In women with a tumour smaller than 10 cm, only 2% of the women with a benign frozen section diagnosis had a false negative diagnosis. Additionally, some authors have reported retrospective studies in which they suggest that the accuracy of frozen section analysis improved when performed by an expert pathologist.[70,71]

Gynaecologists can decide prior to or during surgery whether frozen section analysis will be needed, and they may alter the decision during surgery, depending on the intraoperative findings. Various factors influence the surgeon's use of frozen section analysis, depending on the suspicion of malignancy.[72]

LAPAROSCOPIC EVALUATION OF OVARIAN TUMOURS

Laparoscopy is a common approach for the surgical removal of (presumably benign) ovarian tumours. The decision whether or not to use a laparoscopic approach, is based on the clinical impression of the tumour or its size. Advantages of laparoscopic gynaecologic surgery over laparotomy are: significantly less postoperative pain, fewer adverse events of surgery (surgical injury or postoperative complications), better cosmetic results, and a shorter length of hospital stay.[73] Laparoscopy is, however, associated with an increased rate of intraperitoneal spillage. In malignant tumours this may lead to dissemination of tumour cells, an upgrade in tumour stage, and subsequently a risk of adjuvant chemotherapy needed.[74] An additional concern is the risk of laparoscopic port-site metastases.[75] Nonetheless, a review of literature on the role of minimally invasive surgery in staging of ovarian cancer[76] and a recent retrospective study[77] have concluded that patients with borderline ovarian tumours and apparent early stage ovarian malignancies can safely and effectively undergo laparoscopic surgical management. The studies were conducted in oncology centres and surgeries were performed by trained gynaecologic oncologists.

No protocols have been introduced yet concerning the procedure and interpretation of ovarian tumours during surgery. A standardised examination of an ovarian tumour might improve the value and use of frozen section analysis.

AIMS AND OUTLINE OF THE THESIS

Accurate preoperative diagnosis in women with ovarian tumours is essential for optimal care. In case of doubt, frozen section analysis during surgery helps in making an informed decision in regard to the extent of surgery, preventing both under- and overtreatment. The aims of this thesis are to evaluate opportunities to improve the preoperative and intraoperative diagnosis of ovarian tumours. The objectives are as follows:

1. To verify the effectiveness of the Risk of Malignancy Index in daily clinical practice.
2. To validate an adapted Risk of Malignancy Index.
3. To evaluate the use of frozen section analysis in ovarian tumours.
4. To evaluate whether standardised laparoscopic examination of an ovarian tumour is feasible.

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Evaluation of the Risk of Malignancy Index in daily clinical management of adnexal masses

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ABSTRACT

Objective

To verify the effectiveness of the Risk of Malignancy Index (RMI) in the discrimination between non-invasive (benign and borderline) lesions and invasive malignant adnexal masses in daily clinical practice.

Methods

This prospective observational study was conducted in a multicentre cooperation of 11 hospitals. A total of 548 women with adnexal masses were included. Ultrasound characteristics, menopausal status and serum CA 125 level were registered preoperatively, and combined into the RMI afterwards. Final diagnosis was based on routine histopathologic examination. The decision to have patients operated by or with a gynaecologic oncologist was based on the clinical impression of the gynaecologist in the local hospital, based on physical examination, testing of serum samples, and ultrasound examination. This was compared with the hypothetical situation in which the RMI would have been applied as method of selection.

Results

An RMI of 200 achieved a sensitivity of 81% and specificity of 85% in the detection of ovarian cancer. Positive and negative predictive values were 48% and 96% respectively. In current practice, 64% of ovarian cancer patients were operated by a gynaecologic oncologist. This percentage would have increased to 80% if the RMI with a cut-off value of 200 would have been used as method of selection.

Conclusions

In our study population, introduction of the RMI would improve the management of adnexal masses, with a higher percentage of ovarian cancer patients that are operated by a gynaecologic oncologist. At the same time, referral of patients with non-invasive (benign and borderline) lesions would be reduced.

INTRODUCTION

Ovarian cancer is the leading cause of death from gynaecologic malignancies in The Netherlands. Most cases are diagnosed at advanced stage where prognosis is poor. Several studies have demonstrated that ovarian cancer patients operated by a gynaecologic oncologist are more likely to undergo accurate staging and optimal cytoreductive surgery compared to patients who are operated by general gynaecologists.[1-10] To improve the quality of care, gynaecologic oncologists from academic centres operate in local hospitals on patients with adnexal masses suspect for malignancy in most Dutch regions, following a standardised treatment protocol. The Radboud University Nijmegen Medical Center (RUNMC) has formed such a multicentre cooperation with 10 hospitals in the east of the Netherlands. The decision on whether or not a gynaecologic oncologist needs to be called upon is currently based on the clinical impression of the gynaecologist at the local hospital.

The discriminative preoperative evaluation of adnexal masses is rather complicated. A variety of diagnostic procedures is used, leading to a wide variety of variables which can result in an inaccurate interpretation of the nature of the adnexal mass. Efficiency of care for ovarian cancer patients can be improved by standardizing this preoperative evaluation. Jacobs et al.[11] developed the Risk of Malignancy Index (RMI) for referral of relevant patients to gynaecologic oncologic centres. The RMI was the first diagnostic model that combined demographic, sonographic and biochemical data in the assessment of patients with adnexal masses. The main advantage of this method compared with other diagnostic procedures is that the RMI is a simple scoring system that can be applied directly into clinical practice without the introduction of expensive or complicated methods. The RMI has been adjusted by Tingulstad et al.[12] in 1996 (RMI-2) and again in 1999 (RMI-3).[13] The three versions of the RMI have been validated retrospectively and prospectively in various clinical studies[11-24] where a cut-off value of 200 showed the best discrimination between benign and malignant adnexal masses, with high sensitivity and specificity levels (sensitivity 51–90%, specificity 51–97%).

Two studies[22,25] have included patients in a multicentre study. An important limitation of the study from Bailey et al.[22] is that the study population consisted of patients who had already been referred to the oncologic centre for treatment of a potential ovarian cancer. In the International Ovarian Tumour Analysis Group (IOTA) study,[25] a cut-off value of 100 was used, while 200 is commonly regarded as the most optimal cut-off level. Consequently, the effectiveness of the RMI in clinical application, acknowledging local variations in the serum CA 125 assay and ultrasound expertise, still needs to be assessed.

The aim of the present study was to prospectively verify the effectiveness of the RMI versus clinical impression (of the gynaecologist in the local hospital) to discriminate between non-invasive (benign and borderline) lesions and invasive malignant adnexal masses in daily clinical practice, allowing local variations in serum CA 125 assay and ultrasound expertise.

MATERIALS AND METHODS

This prospective observational study was conducted between January 2005 and January 2008 in the RUNMC, an academic hospital, and 10 cooperating hospitals, all general hospitals, in the east of the Netherlands. Women with adnexal masses, due to be admitted for surgery, were included. Gynaecologists registered the individual parameters of the RMI and returned them on a registration form to the RUNMC. As proposed by Tingulstad et al.[13] in 1999, RMI is defined as the multiplied value of the ultrasound score (*U*), menopausal status (*M*) and serum CA 125 level: RMI=*U*×*M*×CA 125. Multilocularity, solid areas, bilaterality, ascites and intraabdominal metastases score one point each. A total of 2 or more points gives *U*=3, fewer than 2 points gives *U*=1. Postmenopausal status is defined as more than 1 year of amenorrhoea, or age 50 years or older among women who had prior hysterectomies, and scores *M*=3; premenopausal status scores *M*=1. Serum CA 125 (U/mL) is entered directly into the equation. Ultrasound was performed by transvaginal examination and abdominal examination if needed. The ultrasounds were performed by gynaecologic oncologists, general gynaecologists, or gynaecology residents. Serum samples were analysed for CA 125 as part of routine preoperative assessment, and menopausal status was registered. Final diagnoses of included patients were based on the histopathologic examination of surgical specimens. Patients diagnosed with non-gynaecologic malignancies were excluded from the study.

The derived RMI was merely registered and not applied in further planning of care. Based on the clinical impression by the gynaecologist in the local hospital it was decided if a gynaecologic oncologist would be involved in the surgical treatment. This clinical impression was based on the routine preoperative assessment, consisting of physical examination, testing of serum samples, and ultrasound examination. The local gynaecologists varied in levels of expertise, from gynaecologists specialising in oncology to gynaecology residents. It was agreed upon at the beginning of the study that the RMI result would not be used in further decision making. The effect of using the RMI could retrospectively be estimated by creating a hypothetical situation in which the RMI with a cut-off value of 200 would have been applied to decide whether or not an oncologist would be invited to perform the operation. This hypothetical situation was compared with daily clinical practice.

Statistical analyses were performed using the Statistical Packages for the Social Sciences Version 14.0.1 (SPSS Inc., Chicago, IL). Borderline malignancies were allocated to the non-invasive group in all analyses. Comparison between patients with non-invasive (benign and borderline) lesions and invasive malignancies was performed using the Mann–Whitney *U* test for age and serum CA 125 level, the Pearson χ^2 test for menopausal status and the Kruskal–Wallis test for ultrasound score. A receiver operating characteristic (ROC) curve was created to show the relation between sensitivity and specificity of the RMI in the discrimination between non-invasive lesions and invasive malignancies.

RESULTS

A total of 548 patients were included in the study. A number of 415 patients (76%) were diagnosed with benign gynaecologic conditions, whereas 80 patients (14%) had malignant diseases. Borderline malignancies were diagnosed in 53 patients (10%). The distribution of age, menopausal status, ultrasound score and serum CA 125 level in the non-invasive and invasive groups is shown in Table 1. Statistically significant differences between the two groups were observed for all these variables.

Table 1. Distribution of age, menopausal status, ultrasound score and serum CA 125 levels in 548 patients with non-invasive lesions (*n*=468) and invasive malignant (*n*=80) adnexal masses.

Characteristic	Non-invasive lesions (*n*=468)	Invasive malignancies (*n*=80)	Significance level (*p*)
Age (years)			
Median (range)	52 (13-90)	62 (24-89)	0.000[b]
Postmenopausal			
n (%)	254 (54)	60 (75)	0.001[c]
Ultrasound score[a]			0.000[d]
0			
n (%)	132 (28)	3 (4)	
1			
n (%)	177 (38)	12 (15)	
2-5			
n (%)	159 (34)	65 (81)	
Serum CA 125 (U/mL)			
Median (range)	18 (2-1380)	180 (7-3214)	0.000[b]

[a] Ultrasounds were scored one point for each of the following characteristics: multilocularity, solid areas, bilaterality, ascites and intra-abdominal metastases.

[b] Mann-Whitney *U* test.

[c] Pearson χ^2 test.

[d] Kruskal-Wallis test.

The final histopathologic diagnoses are listed in Table 2. The majority of non-invasive gynaecologic conditions included mucinous cystadenomas (n=93) and serous cystadenomas (n=69). Histopathologic diagnoses in invasive malignant diseases were mainly serous cystadenocarcinomas (n=32). In patients with non-invasive gynaecologic conditions the median RMI is 48, with values ranging from 4 to 12420. The median RMI in the invasive malignant group is 1063, with values ranging from 22 to 28926.

Table 2. Distribution of histopathologic diagnoses.

	n	%
Non-invasive lesions (*n*=468)		
Mucinous cystadenomas	93	20
Serous cystadenomas	69	15
Other cystadenomas	10	2
Simple cysts	64	14
Endometriotic cysts	49	10
Dermoids	48	10
Fibroma	45	10
Mucinous borderline	25	6
Serous borderline	16	3
Others	49	10
Invasive malignancies (*n*=80)		
Serous cystadenocarcinomas	32	40
Mucinous cystadenocarcinomas	8	10
Endometrioid adenocarcinomas	10	13
Undifferentiated adenocarcinomas	11	14
Clear cell carcinomas	12	15
Carcinosarcomas	3	4
Granulosa cell tumors	2	2
Others	2	2

The diagnostic performance of the RMI is illustrated in Fig. 1. A cut-off level of 200 gives a sensitivity of 81% and a specificity of 85%. Positive and negative predictive values at that cut-off level are 48% and 96%, respectively.

When comparing the performance of the RMI between premenopausal and postmenopausal patients, premenopausal patients show lower sensitivity (55%) and PPV values (29%) compared to postmenopausal patients (90% and 56% respectively) at a cut-off level of 200. The diagnostic performances of the RMI in these two groups is illustrated in Figs. 2 and 3, respectively.

A total of 70 patients with non-invasive gynaecologic conditions scored an RMI of 200 or more. These cases are considered false positive. The corresponding histopathologic diagnoses are listed in Table 3. A substantial number concerns fibromas (n=15) and endometriotic cysts (n=13). Conversely, 15 patients with invasive malignancies scored an RMI less than 200, and are considered false negative. Corresponding histopathologic diagnoses are also shown in Table 3. Clear cell carcinomas made up 40% of all false-negative cases (n=6). Fifty percent of all clear cell carcinomas which were found in the study had an RMI below 200 (n=6). Two patients presented

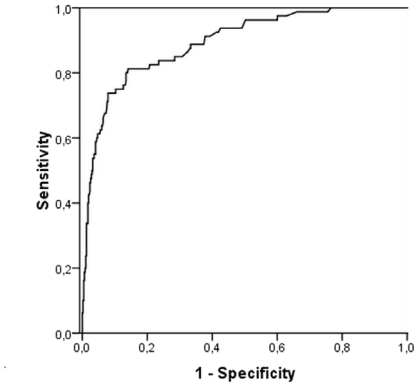

Figure 1. The receiver operating characteristic (ROC) curve of the Risk of Malignancy Index (RMI) applied to the study population (*n*=548). The area under the curve is 0.893.

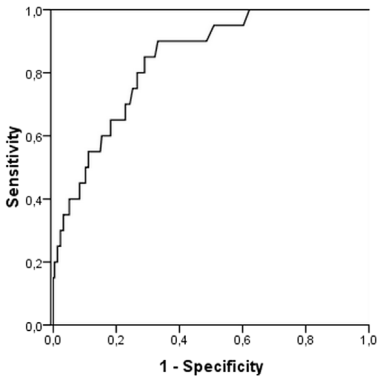

Figure 2. The receiver operating characteristic (ROC) curve of the Risk of Malignancy Index (RMI) in premenopausal patients (*n*=294). The area under the curve is 0.839.

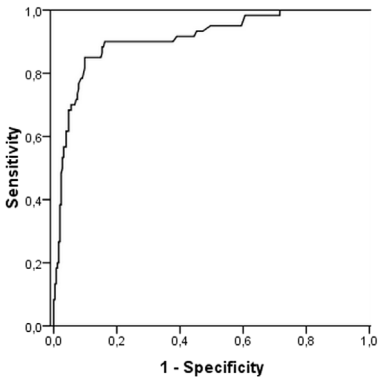

Figure 3. The receiver operating characteristic (ROC) curve of the Risk of Malignancy Index (RMI) in postmenopausal patients (*n*=254). The area under the curve is 0.911.

with multilocularity and solid areas: one being postmenopausal with a CA 125 of 7 U/ml (RMI=63) and the other being premenopausal with a CA 125 of 56 U/ml (RMI=168). Three patients presented with only solid areas on ultrasound: two of them were postmenopausal with CA 125 levels of 23 and 27 U/ml (RMI=69 and 81), the other was premenopausal with a CA 125 level of 22 U/ml (RMI=22). One premenopausal patient presented with only multilocularity on ultrasound and a CA 125 level of 69 (RMI=69).

Table 3. False-positive and false-negative cases with corresponding histopathologic diagnoses.

	n	%
False-positive cases (*n*=70)		
Histopathologic diagnosis		
Endometriotic cysts	13	19
Serous borderline	8	11
Mucinous borderline	7	10
Mucinous cystadenomas	7	10
Other cystadenomas	6	9
Fibroma	15	21
Dermoids	4	6
Other	10	14
False-negative cases (*n*=15)		
Histopathologic diagnosis		
Clear cell carcinomas	6	40
Serous cystadenocarcinomas	3	20
Mucinous cystadenocarcinomas	1	7
Endometrioid adenocarcinomas	2	13
Other adenocarcinomas	2	13
Mullerian adenosarcomas	1	7

The cooperation between the RUNMC and local hospitals is currently based on the clinical impression of the gynaecologist in the local hospital. This current practice was compared with a hypothetical situation, in which the RMI with a cut-off level of 200 would have been applied to decide which patient would be operated by a gynaecologic oncologist. In this way, the effects of using the RMI in clinical practice can be predicted. In current practice, 64% of ovarian cancer patients were operated by a gynaecologic oncologist. This percentage would increase to 80% when the RMI with a cut-off value of 200 would have been used as method of selection. On the other hand, in current practice 56% of operations performed by oncologists concerned non-invasive (benign or borderline) diseases. In the hypothetical situation, referral of these patients would be reduced to 50%.

DISCUSSION

The results of the present study confirm previous publications indicating that the RMI improves the discrimination between non-invasive (benign and borderline) and invasive malignant adnexal masses. The current study population consisted of patients who were preoperatively evaluated without the application of the RMI. Based on the individual clinical impression of the gynaecologist

at the local hospital it was decided if an oncologist from the academic centre was required to perform the operation. By using the registered information, the RMI was derived from the very same study population, to hypothesise how the situation would change when the RMI value was used to determine which patients should be operated by an oncologist. In this manner, the effects of actually applying the RMI can be estimated in a way that to our knowledge has not been published so far. We have thus compared the current practice with the hypothetical situation in which the RMI would have been applied to decide which patient should be operated by an oncologist. In current practice, 64% of ovarian cancer patients were operated by an oncologist. This would increase to 80% when the RMI would be used as method of selection. Most of the extra patients that would have been operated by a gynaecologic oncologist were early stage cases in which proper staging is of great importance. Still these results do not lead to the most optimal situation, because 20% of ovarian cancer patients would not have been operated in an optimal setting even with the introduction of the RMI. The fact that 40% of these "failures" consists of clear cell carcinomas makes this even more problematic. The ability of the RMI to detect different histological types of ovarian malignancies was tested by Aslam et al.[16] in 2000. They found that the RMI performed best in diagnosing invasive epithelial cancer, with a sensitivity of 93%.

Future research on optimising the preoperative discrimination between non-invasive (benign and borderline) and invasive malignant adnexal masses by using new ultrasound techniques or better serum markers could further improve the quality of care.

We acknowledge that an experienced ultrasound examiner can evaluate an adnexal mass with high accuracy by pattern recognition, as has been demonstrated by van Calster et al.[26] They showed in their study that 752 (93%) of the 809 tumours were correctly classified as malignant or benign by pattern recognition. Recently, Yazbek et al.[27] have demonstrated in a prospective randomised controlled study that the quality of gynaecological ultrasonography has a significant influence on the management of patients with suspected ovarian cancer. Experienced sonographers were particularly better in diagnosing benign adnexal pathology. This was based on the evaluation of 150 patients who were already referred to the regional gynaecologic cancer centre. The study did not show how effective the initial referral of relevant patients to the cancer centre was, whereas our present study especially focused on this aspect.

We have chosen to use the RMI as developed by Tingulstad et al.[13] and not the first version as developed by Jacobs et al.[11] The main reason for this is that Jacobs et al. gave an ultrasound score (*U*) of 0 when none of the ultrasound features were present, resulting in an RMI of 0 regardless of the CA 125 level. We consider the CA 125 level as an important parameter of the RMI and therefore decided to use the version as proposed by Tingulstad et al. Recently, Yamamoto et al.[28] published their study in which a fourth RMI was created, that includes tumour size as an additional parameter. The RMI-4 was compared with the previous RMIs and showed improved performance at a cut-off level of 450. It concerns a retrospective study, the RMI-4 still needs to be validated prospectively in different institutions.

Like most previous studies, data from the present study indicate that an RMI of 200 gives the most optimal cut-off value when regarding the entire group of ovarian tumours. Some authors have suggested a different cut-off value.[15,19,24] This is probably a result of a difference in population characteristics: the amount of exceptional and borderline tumours and especially the prevalence of malignancy. For it is well known that, for any test, the positive predictive value will be lower and the negative predictive value higher when used in populations where the disease is uncommon. In our study population, 14% of the patients were diagnosed with invasive malignancies. In hospitals that cover populations with higher prevalences of invasive malignancies, the RMI cut-off value might need to be adjusted. The proposed cut-off value may also be dependent on the region where the RMI is used. When the availability of gynaecologic oncologists is easily arranged, a lower RMI cut-off may be used, to aim for every invasive malignancy to always be operated on by an optimal team. However, when the availability of gynaecologic oncologists is limited, a higher RMI cut-off value may be more convenient.

Borderline malignancies tend to have lower RMI-values compared to invasive malignancies and are therefore less detectable. This can be explained by the different features they exhibit, therefore they have low scores both on ultrasound and CA 125 level.[29] One must keep in mind that the primary goal for developing the RMI is the referral of patients with invasive malignant diseases to gynaecologic oncologists. Some borderline malignancies with invasive implants do require significant gynaecological oncological debulking. The majority of patients with borderline malignancies however do not necessarily have to be operated by a gynaecologic oncologist to optimise their survival chances. Therefore, borderline malignancies were allocated to the non-invasive group when calculating the sensitivity and specificity levels, leaving only invasive malignancies to be detected for referral to a gynaecologic oncologist.

A difference in performance of the RMI was detected when dividing the study population into a pre- and postmenopausal group. The RMI predicted invasive malignancy best in the postmenopausal group. The most important explanation is a different mix of histology in ovarian tumours occurring in pre- and postmenopausal patients, with a higher incidence of ovarian cancer in postmenopausal women. Ovarian enlargements and ovarian masses are furthermore more frequently detected in premenopause, due to e.g. the occurrence of ovulation disorders.[30,31] Secondly, the diagnostic accuracy of serum CA 125 assay is expected to be lower in premenopausal patients. CA 125 levels fluctuate during the menstrual cycle, being the highest during menstruation. Also, diseases such as endometriosis and pelvic inflammatory disease are more frequent in premenopause. These diseases are known to cause elevated CA 125 values.[30] Indeed, our data show that endometriotic cysts make up a substantial amount of false positive cases, due to relatively high CA 125 levels. Although some young patients with endometriosis or other gynaecological conditions that increase the CA 125 level should not be denied the exposure to a gynaecologic oncologist, most benign diseases can be treated by a general gynaecologist.

All CA 125 assays and ultrasounds were performed at the local hospitals. Using different assays for CA 125 analysis reflects clinical practice. This was likewise the case for the ultrasounds which were performed by local gynaecologists. In other studies, the ultrasounds were performed by expert radiologists.[11,14,16] This is preferable in the initial evaluation of a given test, to ensure its reproducibility. It is however the case that in clinical practice, ultrasounds are performed by a variety of gynaecologists with a different expertise. The present study was therefore carried out in the realistic setting of daily practice, not in a controlled study setting that differs from reality.

In conclusion, data from the present study imply that using the RMI increases the percentage of ovarian cancer patients in whom surgery is performed by a gynaecologic oncologist. Moreover, using the RMI may lead to a decrease of the percentage of patients with non- invasive (benign and borderline) lesions where a gynaecologic oncologist was unnecessarily present at the operation. Further research is recommended to determine the actual effect of the use of the RMI in the clinical management of adnexal masses.

CONFLICT OF INTEREST STATEMENT

The authors do not report any potential conflicts of interest.

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External validation of the adapted Risk of Malignancy Index incorporating tumour size in the preoperative evaluation of adnexal masses

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ABSTRACT

Objective

The Risk of Malignancy Index (RMI) is a simple scoring system to standardize and improve the preoperative evaluation of adnexal masses. Since 1990, three versions of the RMI have been validated in various clinical studies. Recently, a fourth version of the RMI (RMI-4) was introduced that includes tumour size as an additional parameter. The aim of this study was to validate the ability of RMI-4 to discriminate between non-invasive lesions and invasive malignant adnexal masses, and to compare its performance with RMI-3.

Study design

Women scheduled for surgery for an adnexal mass between 2005 and 2009 in 11 hospitals were included. Ultrasonographic characteristics, menopausal status and serum CA 125 level were registered preoperatively, and combined into the RMI. The performances of RMI-3 and RMI-4 were assessed and statistically tested for differences.

Result

A total of 643 patients were included: 469 benign, 73 borderline and 101 malignant tumours. The RMI-3 had a sensitivity of 76%, specificity of 82%, positive and negative predictive values (PPV and NPV) of 45% and 95%, and an accuracy of 81%. The RMI-4 had a sensitivity of 74%, specificity of 79%, PPV of 40%, NPV of 94%, and an accuracy of 78%. The accuracy of RMI-3 was significantly higher than the accuracy of RMI-4 (p =.001). Both models had an area under the curve of 0.86.

Conclusion

Both RMI-3 and RMI-4 were able to discriminate between non-invasive lesions and invasive malignant adnexal masses, with similar performances. Including tumour size in the RMI does not improve its performance.

INTRODUCTION

The discriminative preoperative evaluation of adnexal masses is rather complicated. A variety of diagnostic procedures has been used, leading to a wide range of variables which can result in an inaccurate interpretation of the nature of the adnexal mass. In view of treatment of ovarian cysts, the assessment between benign and malignant needs to be performed as accurate as possible. To standardize and improve the preoperative evaluation, Jacobs et al.[1] developed the Risk of Malignancy Index (RMI), which is a simplification of a formula found by logistic regression analysis. The RMI was the first diagnostic model that combined demographic, sonographic and biochemical data in the assessment of patients with adnexal masses. The main advantage of this method compared with other diagnostic models is that the RMI is a simple scoring system that can be applied directly into clinical practice without the introduction of expensive or difficult tools. The original RMI is known as RMI-1. The RMI has been modified by Tingulstad et al. in 1996 (RMI-2)[2] and again in 1999 (RMI-3).[3] The difference between these three measurement tools lies in the different scoring of ultrasound characteristics and menopausal status. The three versions of the RMI have been validated retrospectively and prospectively in various clinical studies[1-15] where a cut-off value of 200 showed the best discrimination between benign and malignant adnexal masses, with high sensitivity and specificity levels (sensitivity 51–90%, specificity 51–97%).

Recently, a fourth RMI was introduced by Yamamoto et al.[16] which includes tumour size as an additional parameter. They found that a cut-off level of 450 in RMI-4 is comparable with a cut-off level of 200 in the three previous RMIs. When they compared the RMI-4 in a retrospective study with 253 cases with the previous RMIs, an improved performance at a cut-off level of 450 was found, with an accuracy of 90%. The RMI-4 still needs to be validated prospectively and in different institutions, to assess external validity. The aim of the present study was to validate the ability of RMI-4 to discriminate between non-invasive lesions and invasive malignant adnexal masses in daily clinical practice, and to compare its performance with RMI-3.

MATERIALS AND METHODS

This study was conducted between January 2005 and September 2009 in the Radboud University Nijmegen Medical Center (RUNMC), a third line regional referral hospital, and in 10 cooperating hospitals in the east of the Netherlands. The study was approved by the medical ethics committee of the RUNMC. The study included 643 women admitted for surgical procedure for an adnexal mass. We have previously published on the RMI-3 in a subgroup of the present study population.[15] Ultrasound was performed transvaginally combined with abdominal ultrasound when needed, by experienced gynaecologic oncologists, general gynaecologists, or registrars in gynaecology. Serum samples were analysed for CA 125 as part of routine preoperative assessment, and menopausal status was registered. Based on the data obtained, the RMI-3 was calculated

prospectively as the multiplied value of the ultrasound score (*U*), menopausal status (*M*) and serum CA 125 level as follows:

RMI-3[3] = *U* x *M* x CA 125. Multilocularity, solid areas, bilaterality, ascites and intra-abdominal metastases score one point each. A total of 2 or more points was recalculated into *U*=3, fewer than 2 points into *U*=1. Postmenopausal status is defined as more than 1 year of amenorrhoea, or age 50 years or older among women who had prior hysterectomies, and scores *M*=3; premenopausal status scores *M*=1. Serum CA 125 (U/mL) was entered directly into the equation.

Based on the obtained data, RMI-4 was calculated retrospectively as follows:

RMI-4[16] = *U* x *M* x *S* x CA 125. A total ultrasound score of 0 or 1 was recalculated into *U*=1, and a score of ≥2 into *U*=4. Premenopausal status scores *M*=1 and postmenopausal status scores *M*=4. The tumour size was obtained from the pathology report. A tumour size (single greatest diameter) of <7 cm was recalculated into *S*=1, and ≥7 cm into *S*=2, as introduced by Yamamoto et al.[16] The serum CA 125 (U/mL) was applied directly to the calculation.

Final diagnoses of included patients were based on the histopathological examination of surgical specimens. Patients that were diagnosed with non-gynaecological malignancies were excluded from the study. The RMI was merely registered and not applied in a standardised manner in the further planning of care. Based on the clinical impression by the gynaecologist in the local hospital it was decided whether a gynaecologic oncologist should be involved in the surgical treatment. This clinical impression was based on routine preoperative assessment, consisting of physical examination, testing of serum samples, and ultrasound examination. The local gynaecologists varied in levels of expertise, from gynaecologists specialised in oncology to general gynaecologists.

Statistical analyses were performed using the Statistical Packages for the Social Sciences Version 16.0.1 (SPSS Inc., Chicago, IL). The sensitivity, specificity, positive and negative predictive values, and accuracy of RMI-3 and RMI-4 were calculated. Borderline malignancies were allocated to the non-invasive group in all analyses. Comparison between patients with non-invasive (benign and borderline) lesions and invasive malignancies was performed using the Mann–Whitney *U* test for age and serum CA 125 level, the Pearson χ^2 test for menopausal status and tumour size and the Kruskal–Wallis test for ultrasound score. A receiver operating characteristic (ROC) curve was created to show the relation between sensitivity and specificity of both RMI-3 and RMI-4 in the discrimination between non-invasive lesions and invasive malignancies, and an area under the curve (AUC) was calculated for both models. The McNemar's test was used to test the difference in performances between RMI-3 and RMI-4. The cut-off level was set at 200 for RMI-3 and 450 for RMI-4 to be able to compare the results with the study of Yamamoto et al.[16] A p-value ≤ .05 was considered as statistically significant.

RESULTS

A total of 643 patients was included in the study, of whom 469 (73%) were diagnosed with benign ovarian cysts, 73 patients (11%) with borderline malignancies, and 101 patients (16%) with malignant diseases. The distribution of age, menopausal status, ultrasound score, tumour size and serum CA 125 level in the non-invasive and invasive groups was as shown in Table 1. Statistically significant differences between the two groups were observed for all these variables.

The histopathological diagnoses are listed in Table 2. The majority of non-invasive gynaecological conditions included mucinous cystadenomas (n=118) and serous cystadenomas (n=86). Histopathological diagnoses in invasive malignant diseases were mainly serous cystadenocarcinomas (n=41).

Table 1. Distribution of age, menopausal status, ultrasound score, tumour size and serum CA 125 levels in 643 patients with non-invasive lesions (*n*=542) and invasive malignant (*n*=101) adnexal masses.

Characteristic	Non-invasive lesions (*n*=542)	Invasive malignancies (*n*=101)	Significance level (*p*)
Age (years)			
Median (range)	55 (13-93)	60 (24-85)	.008[b]
Postmenopausal			
n (%)	327 (60%)	73 (72%)	.023[c]
Ultrasound score[a]			.000[d]
0			
n (%)	129 (24%)	2 (2%)	
1			
n (%)	210 (39%)	19 (19%)	
2-5			
n (%)	203 (37%)	80 (79%)	
Tumour size			.000[c]
<7 cm			
n (%)	204 (38%)	18 (18%)	
≥7 cm			
n (%)	338 (62%)	83 (82%)	
Serum CA 125 (U/mL)			
Median (range)	18 (2-2914)	153 (7-7800)	.000[b]

[a] Ultrasounds were scored one point for each of the following characteristics: multilocularity, solid areas, bilaterality, ascites and intra-abdominal metastases.

[b] Mann-Whitney *U* test.

[c] Pearson χ^2 test.

[d] Kruskal-Wallis test.

The performances of the RMI-3 and RMI-4 at various cut-off levels are presented in Table 3. At a cut-off level of 200, the RMI-3 gave a sensitivity of 76% and a specificity of 82%. Positive and negative predictive values at that cut-off level were 45% and 95%, respectively. The accuracy was 81%. The RMI-4 gave, at a cut-off level of 450, a sensitivity of 74% and a specificity of 79%. Positive and negative predictive values at that cut-off level were 40% and 94%, respectively. The accuracy was 78%.

The diagnostic performances of both RMI-3 and RMI-4 are illustrated in Fig. 1. A comparison of the accuracy levels of the two indices showed that RMI-3 at a cut-off level of 200 was significantly better in predicting invasive malignancy than RMI-4 at a cut-off level of 450 (p=.001). Both models had an area under the curve of 0.86.

Table 2. Distribution of histopathological diagnoses.

	n	**%**
Noninvasive lesions (*n*=542)		
Mucinous cystadenomas	118	22
Serous cystadenomas	86	16
Other cystadenomas	14	3
Simple cysts	66	12
Fibroma	57	11
Dermoids	49	9
Endometriotic cysts	40	7
Mucinous borderline	40	7
Serous borderline	29	5
Others	43	8
Invasive malignancies (*n*=101)		
Serous cystadenocarcinomas	41	40
Mucinous cystadenocarcinomas	10	10
Endometrioid adenocarcinomas	12	12
Undifferentiated adenocarcinomas	15	15
Clear cell carcinomas	14	14
Carcinosarcomas	3	3
Granulosa cell tumors	3	3
Others	3	3

Table 3. Performances of RMI-3 and RMI-4 at various cut-off levels.

Cut-off		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)		Accuracy (%)	
RMI-3	RMI-4	RMI-3	RMI-4	RMI-3	RMI-4	RMI-3	RMI-4	RMI-3	RMI-4	RMI-3	RMI-4
100	350	81	76	68	75	32	36	95	94	70	75
120	400	78	75	76	77	38	37	95	94	76	76
200	450	76	74	82	79	45	40	95	94	81	78
250	500	72	73	86	81	49	41	94	94	84	79
300	550	68	73	87	82	50	43	94	94	84	81

RMI, Risk of Malignancy Index; PPV, positive predictive value; NPV, negative predictive value.

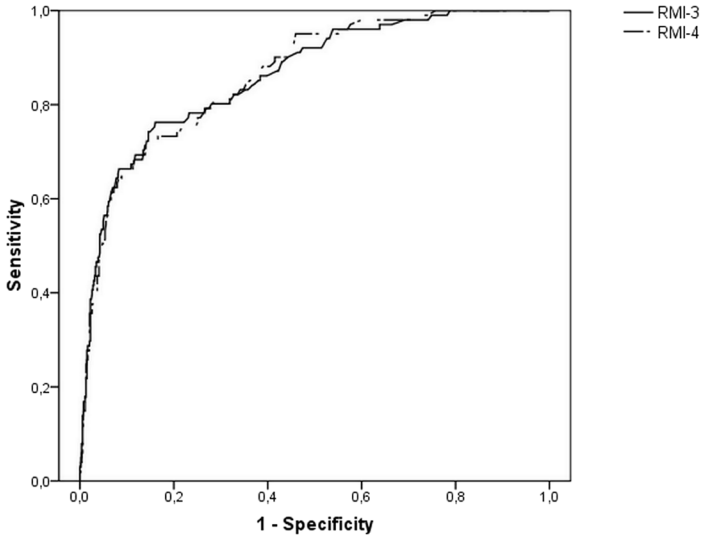

Figure 1. Receiver operating characteristic curves of the Risk of Malignancy Index-3 and Risk of Malignancy Index-4 showing the relation between sensitivity and specificity in the discrimination between non-invasive lesions and invasive malignancies. The area under the curve is 0.86 for RMI-3 and 0.86 for RMI-4.

Footnote: RMI, Risk of Malignancy Index.

COMMENT

This study has confirmed that both RMI-3 and RMI-4 were able to discriminate between non-invasive lesions and invasive malignant masses. The RMI-4 tested on a new population of women with adnexal masses showed lower sensitivity and specificity levels compared with the original report.[16] External validation of proposed models often results in a decreased performance compared to the performance that is reported initially.[8] Therefore, external validation of a prediction model is essential before introduction into clinical practice. In this new population both RMI-3 and RMI-4 were able to discriminate between non-invasive lesions and invasive malignant adnexal masses, with similar performances. Although the accuracy was higher in RMI-4, the similar AUC and overlapping ROC curves indicate that the differences in performances are not statistically significant.

We have chosen to use the RMI-3[3] over the original RMI[1] or RMI-2.[2] The reason for eliminating RMI-1 is that it gives an ultrasound score (*U*) of 0 when none of the ultrasound features were present. This results in an RMI of 0 regardless of the CA 125 level, whereas we consider the CA 125 level as an important parameter of the RMI. CA 125 level does contribute in both RMI-2 and RMI-3. We decided to use the RMI-3 because it has been evaluated more extensively than RMI-2.

Yamamoto et al.[16] have allocated borderline malignancies to the malignant group, whereas we chose to allocate the borderline tumours to the benign group. The primary goal for developing the RMI is the accurate referral of patients with invasive malignant diseases to gynaecologic oncologists. Although some borderline malignancies with invasive implants may require significant gynaecological oncological debulking, more than 90% of cases are stage I tumours and most cases behave in a benign fashion.[10] Women with these borderline malignancies do not necessarily have to undergo aggressive surgical treatment by a gynaecologic oncologist to optimize their survival chances. This difference in allocation of the borderline tumours however, does not explain the different results between the two studies. When we confer the borderline malignancies as malignant in our dataset, the accuracy of RMI-3 and RMI-4 detoriate to 77% and 76%, respectively. RMI-3 still performs better than RMI-4, but the difference is not statistically significant anymore.

Yamamoto et al.[16] have measured tumour size by ultrasound for each patient, whereas we have extracted this information from the pathology report. In daily clinical practice ultrasound would be used, because this is the only parameter on size that is available preoperatively. Although there is no evidence in literature, measurements by ultrasound and by pathology report are expected to be highly correlated. By applying the RMI-4 retrospectively on our dataset we were able to rapidly produce an external validation on the RMI-4 in a high number of patients. Future analysis in a prospective study may however still be needed to validate the RMI-4 as a new tool.

The additional value of tumour size in predicting ovarian malignancy is debatable. Tumour size is not considered an independent predictor of malignancy in ovarian tumours in literature. Recently, McDonald et al.[17] have assessed several tumour variables for their correlation with malignancy. Tumour size with a cut-off level of 10 cm was statistically related to the risk of malignancy, however it was not indicated as a significant factor after a multivariable analysis. Using the cut-off level of 10 cm for the tumour size variable did not improve the performance of RMI-4 in our study population. Unfortunately, Yamamoto et al. did not explain their decision to add tumour size in the RMI. We do not know if they have performed a multivariable analysis to establish that tumour size is an independent predictor of malignancy. Why they have dichotomised the tumour size variable with a cut-off level of 7 cm is also not known. In our study population, the majority of patients with non-invasive lesions (62%) had a tumour size larger than 7 cm. In case the tumour size is included in the RMI, all these women with benign lesions end with a doubled RMI score compared with the situation where the tumour size was not included in the RMI.

In conclusion, this external validation showed that RMI-3 and RMI-4 perform similar in predicting invasive malignancy. Our findings have reconfirmed the ability of the RMI to discriminate between non-invasive lesions and invasive malignant masses. At this moment, we do not see any advantage in introducing an adapted version of the RMI that includes tumour size in the preoperative assessment of adnexal masses.

CONFLICT OF INTEREST STATEMENT

The authors do not report any potential conflicts of interest.

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Factors influencing the use of frozen section analysis in adnexal masses

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ABSTRACT

Objective

To determine the factors that influence the use of frozen section analysis in adnexal masses and the factors that predict malignancy.

Methods

The study participants were women scheduled for adnexal mass surgery in 11 hospitals between 2005 and 2009. Factors that potentially influenced the use of frozen section analysis and potentially predicted malignancy were studied, such as menopausal status, CA 125 level, ultrasound characteristics, presence of adhesions, and tumour size. We used univariable and multivariable analyses to assess the factors.

Results

A total of 670 patients were included in the study. The frozen section analyses for 323 patients (48%) showed 206 benign, 55 borderline, and 62 malignant adnexal masses. The CA 125 level, locularity of the tumour, and presence of solid areas predicted both the use of frozen section analysis and the presence of malignancy. The presence of adhesions predicted malignancy, but not the use of frozen section analysis. Menopausal status and tumour size predicted the use of frozen section analysis, but not malignancy.

Conclusion

Menopausal status and tumour size are associated with more use of frozen section analysis, but they have not been identified as factors associated with malignancy. Frozen section analysis is useful when the CA 125 levels are greater than 35 units/mL and when there are multilocular tumours, solid areas on ultrasonography, and adhesions revealed during surgery.

INTRODUCTION

Frozen section analysis is widely used in the intraoperative evaluation of adnexal masses, and it is often useful to determine the appropriate surgical strategy. The discriminative preoperative evaluation of adnexal masses is rather complex. Various diagnostic models, such as the Risk of Malignancy Index[1-3], are used in the preoperative work-up. Despite all efforts, the interpretation of the nature of the adnexal mass is often inaccurate. The prospective, randomised, controlled study by Yazbek et al.[4] showed that the quality of gynaecological ultrasonography has a significant influence on the management of patients with suspected ovarian cancer. Experienced sonographers diagnosed benign adnexal pathology more accurately.

Intraoperative pathologic examination aids in making an informed decision for determining the extent of surgery and helps prevent both undertreatment and overtreatment. This is especially important for young women who may be managed conservatively with preservation of fertility.

Frozen section analysis is generally accepted as a reliable method for determining the nature of an adnexal mass. The accuracy in detecting invasive malignancies has been assessed in previous studies. A systematic review by Geomini et al.[5] showed high levels of sensitivity and specificity (71–100% and 98–100%, respectively) for frozen section analysis. In contrast, frozen section analysis of borderline adnexal masses appears to be less accurate. Tempfer et al.[6] presented a pooled analysis of four studies that included 317 women with borderline adnexal masses. The overall sensitivity was 71.1% and the positive predictive value was 84.3%.

It might be wise to analyse frozen sections from all patients with adnexal masses to obtain as much information as possible for determining the optimal surgical procedure. However, analysing frozen sections extends the operating time and thus the duration of anaesthesia. Furthermore, frozen section analysis increases costs and implies a heavier workload for pathologists.

Most gynaecologists decide before surgery whether frozen section analysis is needed, and they may alter the decision during surgery, depending on the intraoperative findings. Various factors influence the surgeon's use of frozen section analysis, depending on the suspicion of malignancy.[7] The objective of this study was to determine the factors that influence the use of frozen section analysis in adnexal masses and the factors that predict malignancy.

MATERIALS AND METHODS

This retrospective cohort study was conducted in the Radboud University Nijmegen Medical Center (RUNMC) and 10 cooperating referral hospitals in the east of the Netherlands between January 2005 and September 2009. The study was approved by the medical ethics committee of the RUNMC. Women who were admitted for surgical treatment of an adnexal mass with unknown histology were included in the study. A subgroup (n=548) of the study population has been described in our previous publication about the Risk of Malignancy Index.[3] The patients for whom frozen section analysis was cancelled were excluded from participation in this study if there was clear evidence of malignancy during the surgical procedure, such as pleural effusions and evidence of distal organ involvement.

Menopausal status was registered. Ultrasonography for assessing the locularity of the tumour, laterality, and presence of solid areas, and the determination of the serum level of CA 125 were all parts of the routine preoperative evaluation. All ultrasonography was performed by experienced sonographers. Ultrasonography was performed transvaginally and was combined with abdominal ultrasonography if necessary. Doppler flow studies were not performed. No ultrasound morphologic grading system was used. The presence of adhesions and the diameter of the tumour were retrospectively obtained from the surgery and pathology reports. The use of frozen section analysis was registered, as was the corresponding histopathologic outcome. The final diagnosis of the adnexal mass was based on the full histopathologic examination of all surgical specimens removed. A total of six pathology units covered the pathology activities of the 11 hospitals that participated in this study. One of these units covered four hospitals, two units each covered two hospitals, and three units each covered one hospital.

The histopathologic diagnosis of the frozen section analysis was compared with the final histopathology. The sensitivity, specificity, and the positive and negative predictive values of frozen section analysis for malignant tumours were calculated. Factors that potentially influenced the use of frozen section analysis and potentially predicted the presence of malignancy, including menopausal status, CA 125 level, ultrasound characteristics, presence of adhesions, and tumour size, were studied. We used univariable logistic regression to study the ability of the variables to predict the use of frozen section analysis and to predict invasive malignancy in patients with adnexal masses. We used multivariable logistic regression with stepwise selection procedures to identify variables that contributed independently to the use of frozen section analysis and to the presence of invasive malignancy. All variables that reached the level of significance at 0.10 in the univariable logistic regression were valid for entry in the selection procedure, and we used P=.05 for staying in the model. We used SPSS 16.0.1 for Windows for all statistical analyses.

RESULTS

During the study period, 722 women underwent surgery for an adnexal mass, and 670 (93%) were included in the study. The 52 women (7%) for whom frozen section analysis was cancelled because of clear evidence of malignancy during the surgical procedure were excluded from the study. Of the 670 participants, 531 (80%) had benign gynaecological conditions diagnosed (i.e., final histopathologic diagnosis), 70 (10%) had borderline malignancy diagnosed, and 69 (10%) had malignant disease diagnosed. General gynaecologists performed the surgery for 503 women (75%), gynaecologic oncologists performed the surgery for 53 women (8%), and either a general gynaecologist or a gynaecologic oncologist performed the surgery for 114 women (17%).

Frozen sections were analysed for 323 patients (48%); 206 of these sections (64%) showed benign ovarian cysts, 55 (17%) showed borderline malignancies, and 62 (19%) showed malignant adnexal masses. Frozen sections were analysed for 39% of the benign ovarian cysts, for 79% of the borderline malignancies, and for 90% of the malignant adnexal masses. Table 1 presents the characteristics and final histologic types of all the cases in relation to frozen section analysis.

The adnexal masses of seven patients without frozen section analysis were identified as malignant only after the final histopathologic examination (10%). Five of these patients were postmenopausal and two were premenopausal. Three of the seven patients presented with a multilocular mass and solid areas on ultrasonography. One of them had a CA 125 level of 60 units/mL, and another presented with adhesions during surgery. Two patients presented with multilocularity only on ultrasonography. One patient presented with solid areas only on ultrasonography and one presented with only a CA 125 level of 40 units/mL.

Table 2 shows the comparison of frozen section analysis with the final histopathologic diagnosis. The frozen section analysis was concordant with the final pathology findings for 292 patients (90%). The sensitivity, specificity, and positive and negative predictive values of frozen section analysis were 84% (95% confidence interval [CI] 75–93%), 99% (95% CI 98–100%), 95% (95% CI 89–100%), and 96% (95% CI 94–98%), respectively, for malignant tumours. The accuracy was 96% (95% CI 94–98%).

Table 3 shows factors that potentially influence the use of frozen section analysis or predict the presence of malignancy. In a univariable analysis, all factors tested were significant predictors of the use of frozen section analysis. Predictive factors for the presence of malignancy were the CA 125 level, locularity of the tumour, bilaterality, presence of solid areas, presence of adhesions, and diameter of the tumour.

Table 1. Characteristics and final histopathologic classification in the groups of women with and without frozen section analysis performed.

Characteristic	Total (N=670)	Frozen section analysis performed (*n*=323)	Frozen section analysis not performed (*n*=347)
Age (y)	54 (13-93)	58 (13-93)	50 (16-87)
Postmenopausal	390 (58)	217 (67)	173 (50)
Serum CA 125 (units/mL)	20 (2-2,914)	29 (3-2,914)	14 (2-442)
Histopathologic type			
Benign	531 (80)	206 (40)	325 (60)
Mucinous cystadenomas	124	69 (56)	55 (44)
Serous cystadenomas	92	32 (35)	60 (65)
Other cystadenomas	12	6 (50)	6 (50)
Simple cysts	78	19 (24)	59 (76)
Endometriotic cysts	57	16 (28)	41 (72)
Dermoids	56	14 (25)	42 (75)
Fibroma	56	34 (61)	22 (39)
Other benign diseases	56	16 (29)	40 (71)
Borderline	70 (10)	55 (79)	15 (21)
Mucinous borderline	37	29 (78)	8 (22)
Serous borderline	28	21 (75)	7 (25)
Other borderlines	5	5 (100)	0 (0)
Malignant	69 (10)	62 (90)	7 (10)
Serous cystadenocarcinomas	24	21 (88)	3 (12)
Mucinous cystadenocarcinomas	8	7 (88)	1 (12)
Endometrioid adenocarcinomas	12	12 (100)	0 (0)
Undifferentiated adenocarcinomas	5	4 (80)	1 (20)
Clear cell carcinomas	12	11 (92)	1 (8)
Carcinosarcomas	2	2 (100)	0 (0)
Granulosa cell tumours	3	3 (100)	0 (0)
Other invasive malignancies	3	2 (67)	1 (33)

Data are median (range) or *n* (%).

Table 2. Frozen section analysis and final histopathologic diagnosis in women with adnexal masses.

	Frozen section analysis				
Final histopathology	**Malignant**	**Borderline**	**Benign**	**Undecided**	**Total**
Malignant	52 (84)	7 (11)	2 (3)	1 (2)	62
Borderline	2 (4)	42 (76)	10 (18)	1 (2)	55
Benign	1 (1)	7 (3)	198 (96)	0 (0)	206
Total	55	56	210	2	323

Data are *n* (%) or *n*.

Table 3. Crude odds ratios with 95% confidence interval of variables predicting the use of frozen section analysis and predicting invasive malignancy in women with adnexal masses using univariable logistic regression.

		Frozen section analysis performed		Invasive malignancy*	
Variable	**Total N**	***n* (%)**	**OR (95% CI)**	***n* (%)**	**OR (95% CI)**
Menopausal status					
Premenopausal	280	106 (38)	1.00 (reference)	22 (8)	1.00 (reference)
Postmenopausal	390	217 (56)	2.06 (1.51-2.82)	47 (12)	1.61 (0.94-2.73)
CA 125					
Less than 35 units/mL	455	171 (38)	1.00 (reference)	17 (4)	1.00 (reference)
35 units/mL or more	207	150 (72)	4.37 (3.05-6.26)	51 (25)	8.42 (4.72-15.02)
Locularity of the tumour					
Unilocular	277	89 (32)	1.00 (reference)	16 (6)	1.00 (reference)
Multilocular	393	234 (60)	3.11 (2.25-4.29)	53 (14)	2.54 (1.42-4.55)
Laterality of the tumour					
Unilateral	604	282 (47)	1.00 (reference)	55 (9)	1.00 (reference)
Bilateral	66	41 (62)	1.87 (1.11-3.16)	14 (21)	2.69 (1.40-5.16)
Presence of solid areas					
No	330	103 (31)	1.00 (reference)	11 (3)	1.00 (reference)
Yes	340	220 (65)	4.04 (2.93-5.58)	58 (17)	5.97 (3.07-11.59)
Presence of adhesions					
No	425	192 (45)	1.00 (reference)	29 (7)	1.00 (reference)
Yes	218	123 (56)	1.57 (1.13-2.18)	37 (17)	2.79 (1.67-4.68)
Diameter of the tumour					
Smaller than 5 cm	120	23 (19)	1.00 (reference)	3 (3)	1.00 (reference)
5 – 10 cm	199	63 (32)	1.95 (1.13-3.37)	14 (7)	2.95 (0.83-10.49)
10 – 25 cm	242	183 (76)	13.08 (7.62-22.47)	44 (18)	8.67 (2.63-28.54)
25 cm or larger	42	38 (91)	40.07 (12.99-123.54)	3 (7)	3.00 (0.58-15.48)

OR, odds ratio; CI, confidence interval.

*Based on the full histopathologic examination of all surgical specimens removed.

Table 4 shows the multivariable regression analyses used to identify independent predictive factors for frozen section analysis use and for the presence of malignancy. The CA 125 level, locularity of the tumour, and the presence of solid areas were predictors of both the use of frozen section analysis and the presence of malignancy. The presence of adhesions predicted malignancy, but not the use of frozen section analysis. In contrast, menopausal status and tumour size were predictors of the use of frozen section analysis, but not of malignancy.

Table 4. Adjusted odds ratios with 95% confidence interval of variables predicting the use of frozen section analysis and predicting invasive malignancy in women with adnexal masses using multivariable logistic regression with stepwise selection procedures.

	Frozen section analysis performed	**Invasive malignancy***
Factor	**OR (95% CI)**	**OR (95% CI)**
Menopausal status		Not selected
Premenopausal	1.00 (reference)	
Postmenopausal	1.98 (1.26-3.12)	
CA 125		
Less than 35 units/mL	1.00 (reference)	1.00 (reference)
35 units/mL or more	3.44 (2.09-5.65)	6.62 (3.46-12.82)
Locularity of the tumour		
Unilocular	1.00 (reference)	1.00 (reference)
Multilocular	2.23 (1.43-3.45)	2.56 (1.15-4.42)
Presence of solid areas		
No	1.00 (reference)	1.00 (reference)
Yes	4.42 (2.85-6.90)	3.73 (1.79-7.75)
Presence of adhesions	Not selected	
No		1.00 (reference)
Yes		2.20 (1.21-4.00)
Diameter of the tumour		Not selected
Smaller than 5 cm	1.00 (reference)	
5–10 cm	1.10 (0.99-3.28)	
10–25 cm	10.38 (5.69-18.97)	
25 cm or larger	32.72 (9.97-107.36)	

OR, odds ratio; CI, confidence interval.

The variables valid for entry in the model in both selection procedures were menopausal status, CA 125 level, locularity of the tumour, laterality of the tumour, presence of solid areas, presence of adhesions, and diameter of the tumour.

* Based on the full histopathologic examination of all surgical specimens removed.

DISCUSSION

Intraoperative frozen section analysis is an important and reliable tool in the clinical management of patients with adnexal masses. The main problem in this management is the risk of malignancy, which is why adnexal masses have to be carefully assessed before surgery. As reported in previous publications,[5,8,9] frozen section analysis is a reliable method for detecting invasive malignancies during the operative procedure. In our study, we found high levels of sensitivity (84%) and positive predictive value (95%), which are comparable with those of previous studies.[5,8,9] Little information has been published concerning the factors that influence the decision to analyse a frozen section during adnexal mass surgery. We therefore have investigated which factors influence the use of frozen section analysis in adnexal masses and which factors predict malignancy.

In the recent study by Brun et al.,[7] patient age older than 50 years, tumour size larger than 10 cm, and preoperative evidence of malignancy were associated with more use of frozen section analysis. We also have identified tumour size as an independent predictive factor for using frozen section analysis. Other factors influencing the use of frozen section analysis in our study were the CA 125 level, locularity of the tumour, and presence of solid areas. Tumour size predicted the use of frozen section analysis, but not the presence of malignancy. This is compatible with the literature, because tumour size is generally not considered an independent predictor of malignancy.[10]

In our cohort, frozen sections were more often analysed for postmenopausal women, but menopausal status was not identified as an independent predictor of malignancy. This conflicts with data on the Risk of Malignancy Index that identified postmenopausal status as an independent risk factor for malignancy.[1] Women for whom frozen section analysis was cancelled because of clear evidence of malignancy during the surgical procedure were excluded from the study. These women, however, were more often postmenopausal than the women in our study group (83% compared with 58%). This might have caused a selection bias. Furthermore, it might be possible that menopausal status would have been identified as an independent predictor of malignancy in a larger sample size. Adhesions revealed during surgery were associated with malignancy. However, adhesions did not lead to more use of frozen section analysis. The presence of adhesions is the only variable that cannot be assessed reliably preoperatively; it has to be assessed during surgery. Although we do not have all the necessary information, the data suggest that the decision to analyse a frozen section is more often based on the preoperative findings than intraoperative ones, or that the presence of adhesions is an underestimated predictor of malignancy.

Unfortunately, whether ascites was present was unknown for 68% of the patients. Therefore, we were unable to determine whether the presence of ascites is a predictor of analysing frozen sections to determine malignancy. The presence of ascites could indicate malignancy and probably has an effect on the management of these cases.

The malignancies of seven patients (which represent 10% of all malignancies) were not found intraoperatively. Six of these patients were wrongly diagnosed with benign diseases; therefore, they were not properly staged. Analysing frozen sections would have been of great value in these cases. The surgeon suspected malignancy in one case but decided that the patient would not be a suitable candidate for radical surgery. Therefore, minimally invasive surgery was performed and several biopsies were performed. In this case, frozen section analysis would not have changed the management approach.

Frozen section analysis has its limitations. It is not accurate in all cases. A report by Geomini et al.[11] showed that tumour size has an effect on the accuracy of frozen section analysis. For masses with a diameter of 10 cm or larger, a benign result of the frozen section analysis was less reliable than for masses with a diameter of less than 10 cm. In the group with masses of 10 cm or more, 11% of the women for whom frozen section analysis indicated a benign cyst turned out to have a malignant or borderline tumour according to the final pathology. Not only tumour size but also the mucinous histologic type limits the accuracy of frozen section analysis.[5,9,12,13]

Frozen section analysis is not always useful. If the probability of malignancy is low before surgery, then it is unlikely that frozen section analysis will change the clinical management. This is also true when the malignancy becomes evident before or during surgery. It is important that the use of frozen section analysis is considered carefully in each case to avoid superfluous testing, but it also should be used when necessary to determine the extent of the surgical procedure.

In conclusion, menopausal status and tumour size are associated with more use of frozen section analysis, but they have not been identified as factors associated with malignancy. The frozen section analysis is useful when the CA 125 levels are greater than 35 units/mL and when there are multilocular tumours, solid areas on ultrasonography, and adhesions revealed during surgery.

FINANCIAL DISCLOSURE

The authors did not report any potential conflicts of interest.

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Use of Risk of Malignancy Index to indicate frozen section analysis in the surgical care of women with ovarian tumours

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ABSTRACT

Objective

To evaluate the importance of the Risk of Malignancy Index (RMI) in the decision to perform frozen section analysis among women with ovarian tumours.

Methods

A retrospective study was conducted in 11 centres in the Netherlands. Women who underwent surgical treatment of an ovarian mass with unknown histology between January 2005 and September 2009 were included. The RMI was calculated retrospectively. Frozen section analysis and RMI values were assessed for patients with benign, borderline, and malignant ovarian tumours on final histopathology.

Results

Overall, 670 women were included. Frozen sections were performed in 323 (48.2%) patients, of whom 206 (63.8%) were diagnosed with benign ovarian tumours, 55 (17.0%) with borderline tumours, and 62 (19.2%) with malignant tumours. Overall, 109 (16.3%) women had an RMI below 20, 106 (97.2%) of whom had benign histology results. Among 235 patients with an RMI over 100, 3 (1.3%) postmenopausal women had malignancies that were missed because frozen sections were not performed.

Conclusion

Women with an RMI below 20 have a low risk of malignancy and therefore do not require frozen section analysis. Postmenopausal women with an RMI greater than 100 should be referred to centres where frozen sections can be performed, and proper facilities and expertise are available to perform staging procedures if necessary.

INTRODUCTION

The differentiation between benign and malignant histology is crucial in the management of women with ovarian tumours. Along with surgical expertise, accurate histological assessment before surgery, which usually includes ultrasonography, is important in counselling and preoperative planning of the surgical approach. The Risk of Malignancy Index (RMI)—the first simple diagnostic index suitable for use in clinical practice and which defines the optimal combination of diagnostic criteria—was developed by Jacobs et al.[1] to standardize and improve the preoperative evaluation of ovarian tumours. A RMI cut-off value of 200 is generally used to discriminate between benign and malignant ovarian tumours.

Among women with ovarian cancer, surgical staging and optimal cytoreductive surgery are essential and result in improved survival.[2,3] If the ovarian tumour is benign, a more conservative approach—e.g. one-sided salpingo-oophorectomy or cystectomy—will suffice and can contribute to fertility preservation for young women. Nevertheless, despite careful interpretation, current diagnostic procedures do not allow a definitive diagnosis of ovarian cancer to be established preoperatively, merely suggest its presence instead.[4,5] Frozen section analysis could assist in informed decision making to determine the extent of surgery required and prevent undertreatment or overtreatment. Because of its utility and the limited value of preoperative diagnostics, frozen section analysis is frequently used for ovarian tumours. Indeed, the recommended rate of frozen section analysis in general surgical practice is 5%–15%,[6,7] whereas for ovarian tumours, rates range from 19% to 66%.[8-10]

The accuracy of frozen section analysis is generally good and has been thoroughly assessed in previous studies.[11-13] A systematic review by Geomini et al.[11] showed that frozen section analysis achieves a sensitivity of 71%–100% and a specificity of 98%–100% in malignancy detection. By contrast, frozen section analysis of borderline adnexal masses[13,14] and mucinous histologic tumour types,[11,15] seems to be less accurate. In 2012, Cross et al.[16] used frozen section analysis for suspected early ovarian cancer and showed an excellent diagnostic test accuracy, concluding that frozen section analysis assisted gynaecologic oncologists to perform the appropriate surgery in 95% of cases. Nevertheless, it should be noted that their study population consisted of women with an RMI of 200 and higher. Further, some retrospective studies[17,18] have suggested that the accuracy of frozen section analysis improves when performed by an expert pathologist.

The objective of the present study was to evaluate the importance of the RMI in the decision to perform frozen section analysis among women with ovarian tumours.

MATERIALS AND METHODS

A retrospective study was conducted in Radboud University Medical Center (Radboudumc) and 10 cooperating community hospitals in the east of the Netherlands. Women who were admitted for surgical treatment of an ovarian mass with unknown histology between January 1, 2005, and September 30, 2009, were included. Women in whom clear evidence of malignancy was found before or during the surgical procedure (e.g. pleural effusions and evidence of distal organ involvement) were excluded. Part of this study population has been previously described.[19-21] The study was approved by the medical ethics committee of the Radboudumc. Written informed consent was not required because data were abstracted retrospectively from patient files and stored anonymously in a database.

Transvaginal ultrasonography, combined with abdominal ultrasonography when needed, was performed by experienced echoscopists (all medical doctors). Routine preoperative assessment included analysis of serum samples for cancer antigen 125 (CA 125), and menopausal status was recorded. Patient RMI parameters were registered by gynaecologists as was requested for a previous study.[19] The RMI was calculated as the multiplied value of the ultrasonography score (*U*), menopausal status (*M*), and serum CA 125 level (U/mL) as described by Tingulstad et al.:[22]

RMI = *U* × *M* × CA 125. With regard to *U*, multilocularity, solid areas, bilaterality, ascites, and intra-abdominal metastases were scored as one point each; *U* = 3 was assigned to a total of 2 or more points and *U*=1 to fewer than 2 points. With regard to *M*, a postmenopausal status was defined as more than 1 year of amenorrhea or age 50 years or older among women who had prior hysterectomies, and was assigned a score of *M*=3, whereas premenopausal status scores were assigned as *M*=1. Serum CA 125 values were entered directly into the equation. Of note, the present study was conducted during a period in which the RMI was not used in routine clinical work-up, and was therefore calculated retrospectively from the registered parameters. This allowed a comparison of the results of clinical practice with a hypothetical situation in which the RMI would have been included in clinical management.

The decision to perform frozen section analysis was made by the surgeon on the basis of the suspicion of ovarian malignancy before or during surgery. The complete ovary or the ovarian cyst was sent fresh to the on-site laboratory of the Department of Pathology, to a centralized pathology department in another hospital, or was analysed on-site in an adapted setting during surgery by a pathologist from a centralised pathology department. The most suspicious parts of the tumour were selected for frozen section analysis. Final diagnosis of the tumour was based on full histopathologic examination of all surgical specimens removed. The pathologist who examined the paraffin slides was not masked to the frozen section diagnosis. Histology results from both frozen section analysis and paraffin (final) diagnosis were expressed as benign, borderline, or malignant. Borderline malignancies were allocated to the benign group for calculation of diagnostic performance of frozen section analysis. A total of six pathology

units covered the pathology activities of the 11 hospitals that participated in this study. One of these units covered four hospitals, two units covered two hospitals, and three units covered one hospital.

To evaluate the significance of the RMI in the decision to perform frozen section analysis, frozen section rates for benign, borderline, and malignant ovarian tumours (i.e. final histopathologic diagnosis) were calculated for various categories of RMI values. Descriptive statistics were performed to describe and present the data quantitatively. SPSS 16.0.1 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

A total of 724 women underwent surgery for an adnexal mass during the study period. One hospital (out of the 11 participating hospitals) only had two registered patients and was therefore excluded from further analyses. For 52 (7.2%) women, frozen section analysis was not performed because of clear evidence of malignancy before or during the surgical procedure, and these women were therefore excluded from the study. Of the remaining 670 women, 531 (79.3%) had benign conditions as the final histopathologic diagnosis, 70 (10.4%) had borderline tumours, and 69 (10.3%) had malignant disease. Median age was 54 years (range 13–93) and 390 (58.2%) were postmenopausal. Median serum CA 125 was 20 U/mL (range 2–2914).

Frozen sections were performed in 323 (48.2%) patients, most of whom were diagnosed with benign ovarian tumours (Table 1). Among 169 mucinous tumours, frozen sections were performed for 105 (62.1%). By contrast, among all 501 other histologic types, frozen sections were performed for 218 (43.5%). When frozen sections were performed, 58 (93.5%) of 62 patients with ovarian cancer were properly staged, compared with 6 (85.7%) of 7 for whom no frozen sections were performed.

Table 2 presents the results of frozen section analysis compared with the final histopathologic diagnosis. The sensitivity, specificity, and positive and negative predictive values of frozen section analysis were 85.2% (95% confidence interval [CI] 74.7%–93.3%), 98.8% (95% CI 97.8%–100%), 94.5% (95% CI 89.1%–100%), and 96.7% (95% CI, 93.6%–98.4%), respectively, for malignant tumours. The accuracy was 96.2% (95% CI, 93.8%–98.2%).

Table 1. Final histopathologic classification and use of frozen section analysis in ovarian lesions.

Final histopathology	Total (N=670)	Frozen sections performed (*n*=323)	No frozen sections performed (*n*=347)
Benign[a]	531/670 (79.3)	206/323 (63.8)	325/347 (93.7)
Mucinous cystadenomas	124/531 (23.4)	69/206 (33.5)	55/325 (16.9)
Serous cystadenomas	92/531 (17.3)	32/206 (15.5)	60/325 (18.5)
Cystadenomas NOS	146/531 (27.5)	41/206 (19.9)	105/325 (32.3)
Endometriotic cysts	57/531 (10.7)	16/206 (7.8)	41/325 (12.6)
Dermoids	56/531 (10.5)	14/206 (6.8)	42/325 (12.9)
Fibroma	56/531 (10.5)	34/206 (16.5)	22/325 (6.8)
Borderline	70/670 (10.4)	55/323 (17.0)	15/347 (4.3)
Mucinous borderlines	37/70 (52.9)	29/55 (52.7)	8/15 (53.3)
Serous borderlines	28/70 (40.0)	21/55 (38.2)	7/15 (46.7)
Borderline NOS	5/70 (7.1)	5/55 (9.1)	0
Malignant	69/670 (10.3)	62/323 (19.2)	7/347 (2.0)
Serous adenocarcinomas	29/69 (42.0)	25/62 (40.3)	4/7 (57.1)
Mucinous adenocarcinomas	8/69 (11.6)	7/62 (11.3)	1/7 (14.3)
Endometrioid adenocarcinomas	12/69 (17.4)	12/62 (19.4)	0
Clear cell carcinomas	12/69 (17.4)	11/62 (17.7)	1/7 (14.3)
Other malignancies	8/69 (11.6)	7/62 (11.3)	1/7 (14.3)

NOS, not otherwise specified.

Values are given as number/total number (percentage).

[a]Diagnosis is based on the final histopathologic examination of all surgical specimens removed.

Table 2. Final histopathologic diagnosis by frozen section analysis among women with ovarian lesions.

Final histopathologic diagnosis	Malignant	Borderline	Benign
Malignant (*n*=61)	52 (85.2)	7 (11.5)	2 (3.3)
Borderline (*n*=54)	2 (3.7)	42 (77.8)	10 (18.5)
Benign (*n*=206)	1 (0.5)	7 (3.4)	198 (96.1)
Total (*n*=321)	55 (17.1)	56 (17.4)	210 (65.4)

Values are given as number (percentage).

In two cases, frozen section analysis was undecided.

Women with an RMI value below 20 were mostly diagnosed with benign disease on final histopathology (Table 3). Few women with an RMI value below 20 had frozen sections performed. Among 326 women with an RMI value between 20 and 100, 127 (39.0%) had frozen sections performed, of which 14 (11.0%) showed malignancies on final histopathology. Four (1.2%) women with an RMI value between 20 and 100 had malignant disease, and did not have frozen sections performed. Histopathologic types included one clear cell carcinoma, one serous adenocarcinoma, one mucinous adenocarcinoma, and one metastasised thyroid cancer. A total of 88 (13.1%) women had a RMI value between 100 and 200. Frozen sections were performed for 50 (56.8%) of these women, of which 3 (6.0%) showed malignant disease on final histopathology. Two (2.3%) women with an RMI value between 100 and 200 did not have frozen sections performed and were diagnosed with ovarian cancer (one serous adenocarcinoma and one adenocarcinoma not otherwise specified) on final histopathology. Among 147 women with a RMI value of more than 200, most had frozen sections performed and 45 (34.1%) showed malignant disease on final histopathology (Table 3).

The 7 (1.0%) patients with ovarian cancer who did not have frozen section analysis were operated by general gynaecologists and, except for one patient, all required a second surgery for proper staging. In these cases, the surgeon was not initially aware of the presence of malignancy and therefore did not perform a proper staging procedure. Five of these missed ovarian cancers were in postmenopausal women.

Table 3. RMI, menopausal status, and final histopathologic classification among women with and without frozen section analysis performed.

RMI and final histopathology	Total (N=670)	Frozen sections performed (*n*=323)	No frozen sections performed (*n*=347)
RMI <20	109 (16.3)	14 (12.8)	95 (87.2)
Premenopausal	83 (76.1)	11 (78.6)	72 (75.8)
Benign[a]	81 (97.6)	10 (90.9)	71 (98.6)
Borderline	2 (2.4)	1 (9.1)	1 (1.4)
Malignant	0	0	0
Postmenopausal	26 (23.9)	3 (21.4)	23 (24.2)
Benign	25 (96.2)	3 (100)	22 (95.7)
Borderline	1 (3.8)	0	1 (4,3)
Malignant	0	0	0
RMI 20 – 60	226 (33.7)	78 (34.5)	148 (65.5)
Premenopausal	89 (39.4)	27 (34.6)	62 (41.9)
Benign	76 (85.4)	18 (66.7)	58 (93.6)
Borderline	10 (11.2)	7 (25.9)	3 (4.8)
Malignant	3 (3.4)	2 (7.4)	1 (1.6)
Postmenopausal	137 (60.6)	51 (65.4)	86 (58.1)
Benign	123 (89.8)	41 (80.4)	82 (95.3)
Borderline	10 (7.3)	7 (13.7)	3 (3.5)
Malignant	4 (2.9)	3 (5.9)	1 (1.2)
RMI 60 – 100	100 (14.9)	49 (49.0)	51 (51.0)
Premenopausal	34 (34.0)	18 (36.7)	16 (31.4)
Benign	24 (70.6)	11 (61.1)	13 (81.3)
Borderline	4 (11.8)	2 (11.1)	2 (12.4)
Malignant	6 (17.6)	5 (27.8)	1 (6.3)
Postmenopausal	66 (66.0)	31 (63.3)	35 (68.6)
Benign	53 (80.3)	22 (71.0)	31 (88.6)
Borderline	8 (12.1)	5 (16.1)	3 (8.5)
Malignant	5 (7.6)	4 (12.9)	1 (2.9)

Table 3. Continued

RMI and final histopathology	Total (N=670)	Frozen sections performed (*n*=323)	No frozen sections performed (*n*=347)
RMI 100 – 140	47 (7.0)	25 (53.2)	22 (46.8)
Premenopausal	18 (38.3)	8 (32.0)	10 (45.5)
Benign	16 (88.9)	6 (75.0)	10 (100)
Borderline	0	0	0
Malignant	2 (11.1)	2 (25.0)	0
Postmenopausal	29 (61.7)	17 (68.0)	12 (54.5)
Benign	24 (82.8)	13 (76.5)	11 (91.7)
Borderline	4 (13.8)	4 (23.5)	0
Malignant	1 (3.4)	0	1 (8.3)
RMI 140 – 200	41 (6.1)	25 (61.0)	16 (39.0)
Premenopausal	11 (26.8)	5 (20.0)	6 (37.5)
Benign	7 (63.6)	2 (40.0)	5 (83.3)
Borderline	3 (27.3)	2 (40.0)	1 (16.7)
Malignant	1 (9.1)	1 (20.0)	0
Postmenopausal	30 (73.2)	20 (80.0)	10 (62.5)
Benign	24 (80.0)	15 (75.0)	9 (90.0)
Borderline	5 (16.7)	5 (25.0)	0
Malignant	1 (3.3)	0	1 (10.0)
RMI ≥200	147 (21.9)	132 (89.8)	15 (10.2)
Premenopausal	45 (30.6)	37 (28.0)	8 (53.3)
Benign	30 (66.7)	22 (59.5)	8 (100)
Borderline	5 (11.1)	5 (13.5)	0
Malignant	10 (22.2)	10 (27.0)	0
Postmenopausal	102 (69.4)	95 (72.0)	7 (46.7)
Benign	48 (47.1)	43 (45.3)	5 (71.4)
Borderline	18 (17.6)	17 (17.9)	1 (14.3)
Malignant	36 (35.3)	35 (36.8)	1 (14.3)

RMI, Risk of Malignancy Index.

Values are given as number (percentage).

[a]Diagnosis is based on the final histopathologic examination of all surgical specimens removed.

DISCUSSION

The present results indicate that women with a RMI value below 20 have a low risk of malignancy and therefore do not require frozen sections to be performed. If a RMI cut-off value of 100 had been used in combination with postmenopausal status, three of the women in the present cohort who did not undergo frozen section analysis would have been diagnosed with malignancies at the time of primary surgery. On the basis of these results, it is recommended that postmenopausal women with a RMI value over 100 should be referred to centre hospitals where frozen sections can be performed and where proper facilities and expertise are available to perform the staging procedures if necessary.

Although frozen section analysis is a useful and reliable method to determine the nature of ovarian tumours,[11-13] its inherent disadvantage is the extension of the total operating time and therewith the duration of anaesthesia. This is especially problematic in hospitals without on-site pathology units, where frozen section analysis might be time-consuming and expensive as a result of the transport of the specimen to centralised pathology departments. In the present study, approximately 13% of patients with an RMI value below 20 had frozen sections performed, which could have been circumvented by applying an RMI cut-off to avoid superfluous frozen section testing in benign diseases.

Notably, the RMI used in the present investigation was as developed by Tingulstad et al.[22] rather than the first version developed by Jacobs et al.,[1] because the latter used an ultrasonography score (*U*) of 0 when none of the ultrasonography features were present, thus resulting in a RMI of 0 irrespective of the CA 125 level. Nevertheless, CA 125 level is considered an important variable in the RMI and was therefore included in the present study as suggested by Tingulstad et al.[22]

Among premenopausal patients, the diagnostic accuracy of serum CA 125 is expected to be lower. Endometriosis, which is frequently diagnosed in premenopausal women, is known to cause elevated CA 125 values.[23] In the present study population, approximately 42% of women were premenopausal, 17% of whom were diagnosed with endometriotic lesions on final histopathology. Median serum CA 125 in this subgroup was 80 U/mL (range 8–868). Of women with endometriotic lesions, 14 (29.2%) had RMI values over 200 and 9 (64.3%) of these underwent frozen section analysis, indicating that women with endometriotic lesions require special attention, as previously emphasized by Daponte et al.[24]

The RMI was previously found to have a sensitivity of 81% and a specificity of 85% for discrimination between benign and malignant ovarian tumours at a cut-off value of 200.[19] In the present study, a total of 523 patients had a RMI value below 200, of whom 23 (4.4%) had a final diagnosis of ovarian cancer; however, on the basis of RMI alone, these patients would probably have been classified as having benign disease, with likely consequences with regard to the extent of surgery. This clearly illustrates the shortcomings of the RMI.

A limitation of the present study is its retrospective nature. Nevertheless, this characteristic does not have an impact on the reliability of the calculated RMI. Because the gynaecologists were asked to register the variables of the RMI preoperatively, the RMI could be reliably calculated postoperatively. Furthermore, all CA 125 assays were performed at all participating centres as part of routine preoperative assessment. Thus, despite the use of different CA 125 assays reflecting clinical practice, this could be a limitation of the study design.

Although the RMI already includes menopausal status, the present results justify the combination of the RMI with menopausal status to further improve the care of women with ovarian tumours. Indeed, the results suggest that a RMI cut-off value of 100 can be used in combination with a postmenopausal status to select patients in whom frozen sections should be performed. If this rule had been applied in the present study population, 29 additional frozen sections would have been performed to diagnose three further patients with malignancies at the time of primary surgery, which is considered an acceptable rate of extra diagnostic work-up. Further prospective research is recommended to determine whether an RMI cut-off value of 100 should be implemented in the clinical management of postmenopausal women with adnexal masses.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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Prediction of ovarian histology by laparoscopic observation

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ABSTRACT

Introduction

The objective was to determine diagnostic accuracy and interobserver agreement of laparoscopic examinations of ovarian tumours, using videotaped laparoscopic procedures.

Material and methods

Retrospective observational study, conducted in the Radboud university medical center, Nijmegen and Máxima Medical Center, Veldhoven, the Netherlands. 10 gynaecologists scored video recordings of laparoscopic examinations of ovarian tumours. Scoring was performed with and without depriving of clinical information. Parameters included: adnex normal/abnormal, presence of adhesions, smooth surface, abnormal vessels, endometriosis, metastases, and free fluid. Clinical impression was classified as (probably) benign or (probably) malignant, and a specific diagnosis was asked for. Borderline tumours were included in the malignant group. Kappa (κ) statistics were used to determine the level of agreement between observers.

Results

41 women were included. Histological diagnoses included 36 (88%) benign, two (5%) borderline, and three (7%) malignant tumours. Scored without clinical information, overall sensitivity of diagnosis of malignancy was 49%, specificity was 95%. With clinical information provided, outcomes were 61% and 94%, respectively. Interobserver agreement of diagnosis of malignancy was moderate and fair in both groups of observers (κ=0.51 and 0.26, respectively). Agreement was best for adhesions and endometriosis (κ=0.71 and 0.60). Agreement for other parameters was poor to fair (κ=-0.02–0.34).

Conclusions

Diagnostic performance of evaluations of videotaped laparoscopic examination of ovarian tumours was evaluated, sensitivities of diagnosis of malignancy were 49-61%. Interobserver agreement of overall clinical impression and most diagnostic features of ovarian tumours were unsatisfactory and therefore not useful for clinical practice yet.

INTRODUCTION

Laparoscopy is a common approach for the surgical removal of (presumably benign) ovarian tumours. Advantages of laparoscopic gynaecologic surgery over laparotomy are: less post-operative pain, less postoperative complications, better cosmetic results, and a shorter length of hospital stay.[1] Minimally invasive surgery has been shown to be safe and effective in the management of uterine and cervical cancer, and is now a common procedure in these malignancies. Laparoscopy in women with ovarian cancer is however associated with an increased rate of intraperitoneal spillage. This may lead to dissemination of tumour cells, an upgrade in tumour stage, and subsequently a risk of chemotherapy needed.[2] An additional concern is the risk of laparoscopic port-site metastases.[3] Nonetheless, a review of the literature on the role of minimally invasive surgery in staging of ovarian cancer,[4] and a recent retrospective study[5] have concluded that women with borderline ovarian tumours and apparent early stage ovarian malignancies can safely and effectively undergo laparoscopic surgical management, when performed in referral centres by trained gynaecologic oncologists.

When an ovarian tumour is detected, it is meaningful to establish whether it is likely to be malignant or benign as this diagnosis will guide decision making on the surgical approach. A number of tools are available to facilitate preoperative diagnosis, such as ultrasonography, tumour markers and prediction models on the risk of malignancy. The Risk of Malignancy Index (RMI), introduced by Jacobs et al.[6] in 1990, was the first simple diagnostic index suitable for use in clinical practice, which defines the optimal combination of ultrasound features, menopausal status, and CA 125 value. In a previous publication,[7] we confirmed an RMI cut-off level of 200 for discrimination between benign and malignant ovarian tumours, which showed a sensitivity of 81% and a specificity of 85%. Several other diagnostic models have been developed since the introduction of the RMI, and some of them performed better, as found in a recent systematic review and meta-analysis.[8] Recent studies suggest the International Ovarian Tumour Analysis Logistic Regression model LR2 or the Simples Rules as the approach of choice when expert ultrasound expertise is not available. Also, several studies have concluded that these approaches maintain their performances in the hands of relatively inexperienced examiners.[9-12]

Due to the heterogeneity of ovarian tumours, the preoperative diagnosis is limited and presence of malignancy cannot be determined with 100% accuracy until histological examination of the surgical specimens. Therefore intraoperative interpretation of ovarian tumours is useful, and has hardly been studied so far. There are also no standardised protocols for laparoscopic interpretation of ovarian tumours (benign, borderline, or malignant). The aim of the present study was to determine the overall diagnostic accuracy and the interobserver agreement of laparoscopic examinations of ovarian tumours with a scoring system, using videotaped laparoscopic procedures.

MATERIAL AND METHODS

This retrospective observational study was conducted in the Radboud university medical center, Nijmegen and Máxima Medical Center, Veldhoven. The study was approved by the medical ethics committee of the Radboud university medical center. Video recordings of laparoscopic examinations of ovarian tumours were assessed independently by 10 observers, including six gynaecologic oncologists, three general gynaecologists, and one fellow in gynaecologic oncology. All observers were experienced laparoscopic surgeons (>100 adnexal laparoscopic surgeries). To simulate clinical practice, specific training with the scoring system before initiation of the study was not performed. Patient information and identification data were removed from each recording prior to scoring to protect patient identity. Eight observers were deprived of clinical information. After initial scoring, six observers were provided with clinical information in a next step and had the opportunity to change their suggested diagnoses. The remaining two observers scored once, with the clinical information provided directly. All observers scored the video recordings independently and separately.

Laparoscopic examination was performed as part of routine clinical practice in women with ovarian tumours. The included patients were operated between February 2009 till February 2012. Inclusion was not consecutive regarding patients with laparoscopy for ovarian tumours, but depended on the availability of video recordings. Consecutive patients with available video recordings were included. The procedure of scoring was standardised and each adnex was scored on a case record form. A case record form was produced for purpose of the study, since no scoring systems were reported in literature. The parameters included: adnex normal/abnormal, presence of adhesions, smooth surface, abnormal vessels, endometriosis, metastases, and free fluid. The observers were asked to classify the tumours as benign, probably benign, probably malignant, or malignant. A specific diagnosis was asked for, using the following categories: cystadenoma; endometriotic cyst; dermoid cyst; follicular cyst or theca lutein cyst; borderline malignancy; ovarian carcinoma; and other. Video recordings were excluded if five of more observers judged them not suitable to score. The final diagnosis of the ovarian tumours was based on the full histopathologic examination of all surgical specimens removed and was considered the gold standard.

The overall diagnostic accuracy of the videotaped observing based diagnosis was analyzed in relation to the presence or absence of a malignancy, in terms of sensitivity and specificity.

Kappa (κ) statistics (Fleiss' multirater κ) with their 95% confidence intervals were used to determine the level of agreement between observers. Agreement was tested both by the overall diagnosis (benign versus malignant) and by the individual diagnostic features of the tumours. When κ equals one, perfect agreement is implied; whereas when κ equals zero, the agreement is no better than that which would be obtained by chance. Kappa values under 0.20 were considered poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; and 0.81–1.00 excellent. We used SPSS 20.0.0.1 for Windows for all statistical analyses.

RESULTS

Video recordings were scored of 41 patients. The median age of the women was 41 years (range 24–69 years); the majority of women (n=29, 71%) were premenopausal. The histologic diagnoses (based on final histopathologic examination) are noted in Table 1 and included 36 (88%) benign, two (5%) borderline, and three (7%) malignant tumours.

Most suggested diagnoses, based on the video recordings, were cystadenoma and endometriotic cysts (63% of all diagnoses). Intra-abdominal metastases were only observed in a few patients by three observers (observer2: n=3; observer5: n=1; observer8: n=1). These observations were incorrect as these cases were classified as benign on final histopathologic examination.

The two serous borderline cases were mostly scored as benign, based on the video recordings. They were diagnosed mainly as cystadenoma (one case by five, the other by four observers). The two serous adenocarcinomas were correctly diagnosed by all observers except two, who each scored one case as not evaluable. The metastasised galbladdercarcinoma was misdiagnosed by all observers. This case was mostly scored as cystadenoma (six observers), and two observers scored this case as borderline malignant.

Table 1. Histological diagnoses of the 41 patients included in the study.

Histological diagnosis[A]	*n*	Correctly scored by observers (overall, %)	Range (%)
Benign			
Endometriotic cyst	15	77	(47-100)
Dermoid	5	26	(0-40)
Simple cyst	6	47	(33-67)
Serous cystadenoma[B]	5	51	(29-86)
Mucinous cystadenoma[B]	2		
Fibroma	3	7	(0-33)
Borderline			
Serous borderline	2	20	(0-50)
Malignant			
Serous cystadenocarcinoma	2	70	(0-100)
Gallbladder carcinoma	1	0	(0-0)

[A] Diagnosis is based on the final histopathologic examination of surgical specimens removed.

[B] Observers scored 'cystadenoma', no further differentiation was asked for.

The observers who were deprived of clinical information and got the opportunity to change their suggested diagnosis after clinical information was provided, stayed with their first suggestion in most (borderline) malignant cases (87%). Two observers correctly diagnosed the borderline cases only after clinical information was provided. One observer scored a borderline case as ovarian carcinoma first and then changed it to endometriosis when provided with clinical information.

Of all benign cases (n=36), 6 (17%) were diagnosed as borderline or malignant, based on the video recordings. These included two endometriotic cysts, two dermoids, one simple cyst and one serous cystadenoma. As to the benign cases, the observers who were deprived of clinical information and got the opportunity to change their suggested diagnosis after clinical information was provided, changed their diagnoses in three cases correctly, and in two cases incorrectly.

Overall sensitivity of diagnosis of malignancy was 49% in observers deprived of clinical information, with a specificity of 95%. Once clinical information was provided the sensitivity and specificity were 61% and 94%, respectively (Table 2). The gynaecologist's subspecialty (gynaecologic oncologist or general gynaecologist) was not related to the accuracy of assessments.

Table 3 presents the interobserver agreements of scored items. The interobserver agreement of diagnosis of malignancy was moderate in observers deprived of clinical information (κ=0.51) and fair in observers provided with clinical information (κ=0.26). Agreement was best for adhesions and endometriosis (κ=0.71 and 0.60). Agreement for the other parameters was poor to fair (κ= -0.02–0.34).

Table 4 presents the frequencies of observed variables in benign and malignant cases by all 10 observers. Smooth surface, adhesions and endometriosis were more frequently observed in benign cases. Numbers were too small to perform statistical analyses.

Table 2a. Overall sensitivity and specificity of the videotaped observing based diagnosis of malignancy, *observers deprived of clinical information.*

Observer	*n*	Sensitivity (%)	Specificity (%)
1	39	60	94
2	40	25	94
3	41	80	94
4	41	40	94
5	40	60	91
6	39	40	100
7	41	40	100
8	38	40	94
Overall	40	49	95

n refers to the number of evaluable cases.

Observers 2, 3, 4, 5, 6 and 7 are gynaecologic oncologists.

Table 2b. Overall sensitivity and specificity of the videotaped observing based diagnosis of malignancy, *observers provided with clinical information.*

Observer	*n*	Sensitivity (%)	Specificity (%)
1	41	60	94
2	30	100	93
3	41	60	100
4	41	40	92
5	40	60	89
6	41	60	100
9	40	60	94
10	40	60	91
Overall	39	61	94

n refers to the number of evaluable cases.

Observers 2, 3, 4, 5 and 6 are gynaecologic oncologists.

Table 3a. Interobserver agreement of specific features of the videotaped laparoscopic evaluations of ovarian tumours, *observers deprived of clinical information.*

Variable	Agreement (%)	Kappa[D]	95% CI[E]
Adhesions	86	0.71	0.65-0.78
Smooth surface	83	0.22	0.15-0.28
Abnormal vessels on surface	66	0.31	0.24-0.37
Endometriosis	80	0.60	0.53-0.67
Intra-abdominal metastases[A]	96	-0.02	-0.10-0.05
Free fluid[A]	70	0.34	0.26-0.43
Clinical impression[B]	93	0.51	0.44-0.57
Specific diagnosis[C]	27	-0.01	0.04-0.04

[A] Scored per patient, not per adnex.

[B] (probably) benign versus (probably) malignant.

[C] Categories: cystadenoma; endometriotic cyst; dermoid cyst; follicular cyst or theca lutein cyst; borderline malignancy; ovarian carcinoma; and other.

[D] Fleiss' multirater kappa

[E] 95% confidence interval

Table 3b. Interobserver agreement of specific features of the videotaped laparoscopic evaluations of ovarian tumours *observers provided with clinical information.*

Variable	Agreement (%)	Kappa[D]	95% CI[E]
Adhesions	78	0.52	0.21-0.83
Smooth surface	87	0.42	0.13-0.72
Abnormal vessels on surface	73	0.22	-0.07-0.52
Endometriosis	87	0.72	0.43-1.00
Intra-abdominal metastases[A]	100*	0.72	0.43-1.00
Free fluid[A]	68	0.19	-0.13-0.50
Clinical impression[B]	82	0.26	-0.05-0.57
Specific diagnosis[C]	-15	-0.45	-0.56-0.35

[A] Scored per patient, not per adnex.

[B] (probably) benign versus (probably) malignant.

[C] Categories: cystadenoma; endometriotic cyst; dermoid cyst; follicular cyst or theca lutein cyst; borderline malignancy; ovarian carcinoma; and other.

[D] Fleiss' multirater kappa.

[E] 95% confidence interval.

*all observers scored 'no' in all cases.

Table 4a. Frequencies of observed variables in benign and malignant cases by observers *deprived of clinical information.*

Variable	Benign[A] *n*=36 Overall observed (%)	Malignant[A] *n*=5 Overall observed (%)
Adhesions	44	36
Smooth surface	89	64
Abnormal vessels on surface	50	55
Endometriosis	38	2
Intra-abdominal metastases	2	0
Free fluid	25	50

n refers to the number of patients.

[A] Diagnosis is based on the final histopathologic examination of surgical specimens removed.

Table 4b. Frequencies of observed variables in benign and malignant cases by observers *provided with clinical information.*

Variable	Benign[A] *n*=36 Overall observed (%)	Malignant[A] *n*=5 Overall observed (%)
Adhesions	36	21
Smooth surface	91	63
Abnormal vessels on surface	20	33
Endometriosis	43	0
Intra-abdominal metastases	2	0
Free fluid	24	50

n refers to the number of patients.

[A] Diagnosis is based on the final histopathologic examination of surgical specimens removed.

DISCUSSION

This study assessed the diagnostic performance of a standardised laparoscopic scoring system, in order to explore whether implementation might improve the quality level of laparoscopic examination of ovarian tumours. To our knowledge this is the first study reporting a method for assessing the quality of laparoscopic examination of ovarian tumours.

Borderline tumours were allocated to the malignant group for the purpose of this study, given the high conversion rate from borderline to malignant on the final histology report.[13] A classification of borderline ovarian tumours as benign lesions would also have been justifiable. Borderline ovarian tumours tend to occur in younger women and they are usually associated with a good long-term prognosis.[14] Therefore, more conservative, fertility-sparing surgery should be carried out on women who are of reproductive age and who have not completed their families. With respect to the present study, the sensitivity of the diagnosis of malignancy would be higher in case borderline tumours had been allocated to the benign group.

One patient was diagnosed with a metastasis of gallbladder carcinoma in an ovary on final histopathology. Preoperative diagnosis was benign, ultrasound showed one enlarged multilocular ovary of nine cm, the other ovary contained solid parts and measured four cm. The patient was postmenopausal and the preoperative serum CA 125 level was 55 units/mL. We did not exclude this case, because the occurrence of secondary malignancies reflects clinical practice and should always be considered to avoid pitfalls in diagnosis and therapy.

The strengths of our study include the number of observers as well as the different subspecialties of the observers. The fact that we used video recordings of laparoscopic examinations may be considered both a strength and a weakness. It may be considered a strength, because the observers were exposed to exactly the same information, and their assessments were not biased by any clinical information. Another benefit of using video recordings is that we did not have to interfere with clinical practice for this observational study.

On the other hand, the use of video recordings may be considered a weakness, because the reproducibility of live laparoscopic examinations might be superior to that of evaluation of video recordings and these results therefore cannot be extrapolated to live examinations. The use of video recordings may not reflect conditions during standard laparoscopic examination of that observer. This could have caused the observers to depart from their usual examination techniques, resulting in inaccuracies in the assessment of different diagnostic features. Providing clinical information (age, menopausal status, laboratory results, findings on ultrasound) did enhance the interpretation of the video recordings in our study, although not drastically. Another weakness is the method of including patients. We depended on the availability of video recordings of laparoscopic procedures and therefore patient inclusion was not consecutive. In future studies, women should be included consecutively for a representative sample of study patients.

Similar studies which have used video recordings include laparoscopic reproducibility studies on the diagnosis of endometriosis, and showed a high degree of variability in reproducibility. Weijenborg et al.[15] assessed the intraobserver and interobserver reliability of videotaped laparoscopic evaluations for endometriosis and adhesions. The authors concluded that the evaluations of videotaped laparoscopies for endometriosis were reliable and justified the use of video recordings. However, in women with endometriosis, observers tended to disagree on the severity and extent of the endometriotic disease. The authors have shown that, regarding adhesions, evaluation during videotaped laparoscopy was not reliable. In our study, the interobserver agreement for presence of adhesions was good (κ=0.71) for observers deprived of clinical information, however adhesions were observed not only in malignant cases (36%) but also in benign cases (44%). Once clinical information was added, interobserver agreement for presence of adhesions was moderate (κ=0.52), and adhesions were observed in 21% of malignant and 36% of benign cases. This does not support the use of presence of adhesions as a reliable sign of malignancy.

Buchweitz et al.[16] also evaluated video recordings of laparoscopic examinations of endometriotic diseases, and found a considerable interobserver variability. A study by Bowman et al.[17] compared scorings of adnexal adhesions during real-time laparoscopy with assessments of videotaped laparoscopies in women who had been diagnosed previously with adhesions. The authors found a large variation in adhesion scorings and a poor level of agreement on subdivisions of adhesion total scores.

Poor to fair interobserver agreement suggests that laparoscopic examination of ovarian tumours would need further evaluation before clinical implementation. Intraoperative histopathologic diagnosis by for example frozen section analysis is obviously still considered necessary and care should be taken to avoid tumour spillage with all adnexal masses. Another implication of poor to fair agreement is that the diagnostic feature warrants attempts to better define its categories. In case better definitions would not result in increased agreement, the feature should not be used as a reliable sign of disease.

In conclusion, this study evaluated diagnostic performance of evaluations of videotaped laparoscopic examination of ovarian tumours. Sensitivities of diagnosis of malignancy were low. The interobserver agreement of the overall clinical impression and most diagnostic features of ovarian tumours used in this study were unsatisfactory and therefore not useful for clinical practice.

CONFLICTS OF INTEREST STATEMENT

The authors do not report any potential conflicts of interest.

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Efficacy of a regional network for ovarian cancer care

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ABSTRACT

Objective

To study the influence of a regional collaboration in epithelial ovarian cancer care on staging procedures, debulking results, and survival.

Methods

In an effort to optimise epithelial ovarian cancer treatment, a regional collaboration was introduced in the Netherlands in 2000. Gynaecologic oncologists from the university centre conducted surgery in community hospitals when ovarian cancer was considered based on the Risk of Malignancy Index or clinical suspicion. The National Cancer Registry registered 1,554 patients with epithelial ovarian cancer diagnosed in 11 participating Dutch hospitals between 1996 and 2010. Surgical procedures were compared during three periods (1996–1999, 2000–2004, and 2005–2009). Log-rank tests compared Kaplan-Meier survival curves of progression-free and overall survival before (1996–2000) and during the start of the collaboration (2001–2005).

Results

Staging was adequate for 139 patients (23.0%) before collaboration, and this proportion increased during the study periods to 32.1% and 62.1% ($P<.01$), when gynaecologic oncologists more often staged cancer in patients (36.7% compared with 54.7% and 80.6%; $P<.01$). For 1,197 patients with advanced stage disease (stage IIb or greater), the proportion of debulking procedures with an optimal (residual volume less than 1 cm) as well as a complete result (no residuals) increased during the 14-year study period from 57.4% to 76.5% ($P<.01$) and from 24.1% to 43.4% ($P<.01$), respectively. Survival rates were similar before and during the start of the collaboration. In multivariable analysis, the treatment variables completeness of debulking, chemotherapy, and gynaecologic oncologist attendance were independent prognostic factors for overall survival, as were age, stage, and tumour grade.

Conclusions

After regional collaboration, gynaecologic oncologists attended more surgeries and surgical outcomes improved, but progress in survival could not be demonstrated. Regional collaboration improved care for ovarian cancer patients.

INTRODUCTION

Epithelial ovarian cancer is the most lethal gynaecological cancer in the developed world, and the prognosis has improved only slightly in recent decades. Changes in chemotherapy regimens achieved progress, but further improvement of survival may be expected from surgical treatment.

A meta-analysis showed that increased cytoreduction is associated with better survival.[1] Complete debulking gives the greatest benefit of surgery.[2,3] A full staging procedure will upstage approximately 30% of the patients with early stage disease.[4,5] It is generally accepted that gynaecologic oncologists perform the surgical procedures more adequately than general gynaecologists,[6,7] which results in better survival.[6,8-10] An overview of the European pattern of care in the 1990s showed that substantial numbers of patients with ovarian cancer were treated suboptimally.[11] At that time in the Netherlands, general gynaecologists treated most patients in the hospital of diagnosis, and still do in many other countries. Initiatives to centralise treatment have been launched in the past 20 years.

Regional collaboration in gynaecologic oncology was introduced in 2000, and 11 hospitals participated. The main goal was to improve care by means of consultations with gynaecologic oncologists when ovarian cancer was suspected. The 11 hospitals cover a region with 1.7 million inhabitants; approximately 110 patients have epithelial ovarian cancer diagnosed annually. The Risk of Malignancy Index (RMI) was implemented in 2005 to improve care with standardised risk assessment for pelvic masses.[12]

The aims of our population-based study were to assess changes that coincide with the introduction of the collaboration and to evaluate the role of the collaboration in care. The attendance of gynaecologic oncologists during surgery, staging and debulking results, and survival of patients are all factors that we compared before and after the regional network was introduced.

MATERIALS AND METHODS

The Institutional Board of the National Cancer Registry and all the gynaecologic departments involved gave their ethical approval for this retrospective population-based study in the east of the Netherlands. All consecutive patients in this region with epithelial ovarian cancer diagnosed between 1 January 1996 and 1 January 2010 were selected from the Netherlands Cancer Registry. This registry is based on the reports of all newly diagnosed malignancies in the automated nationwide pathology archive and the national registry of hospital discharge diagnoses. Trained medical registrars, using a standard case record form, studied the hospital records of the patients. We compared the surgical results of 1996–1999 (before the collaboration) with those of 2000–2004 (during introduction of the collaboration) and 2005–2009 (full introduction of the

collaboration). To allow sufficient follow-up, we studied survival during two calendar periods (1996–2000 and 2001–2005).

The 11 hospitals involved one specialised university centre hosting five gynaecologic oncologists. These gynaecologists completed a fellowship in gynaecologic oncology or are registered as gynaecologic oncologists by the Dutch Society of Obstetrics and Gynaecology (or both). The three teaching hospitals that were involved in the network had two semi-specialising gynaecologists and approximately eight general gynaecologists each. Semi-specialising gynaecologists are not formally trained in oncology, but they treat most of the oncology patients in the larger teaching hospitals. Seven nonteaching general hospitals with four to six general gynaecologists collaborated. The maximum radius from the university medical centre to the satellite hospitals was approximately 100 km.

From 2005 onward, gynaecologists were requested to register the RMI parameters for all patients with adnexal masses for the purpose of a prospective observational study of the effectiveness of the RMI.[12] This index was calculated as the multiplied value of the ultrasound score, menopausal status, and serum CA 125 level, as Tingulstad proposed in 1999.[13] In 2008, it was formally introduced as a tool for selecting patients for surgery performed by a gynaecologic oncologist. A score of 200 or more on the RMI indicated the need for a gynaecologic oncologist. If the score was less than 200, the gynaecologic oncologist only participated when specifically requested.

In agreement with previous studies, we defined the minimal adequate staging as a total abdominal hysterectomy and bilateral salpingo-oophorectomy, infracolic omentectomy, at least one resected lymph node, and one peritoneal biopsy. As the evidence-based Dutch guideline 2009 states,[14] a staging procedure should include resection of at least 10 lymph nodes. We decided to show the results according to our definition as well as the number of lymph nodes. We defined optimal debulking as leaving no residual tumour larger than 1 cm in diameter. Complete debulking constitutes surgery with no macroscopic residual tumour. We analysed the debulking results for patients with advanced stage disease (stage IIb or higher).

We used the Pearson χ^2 and Student *t* test to compare categorical and continuous characteristics. We used survival techniques to study the time to recurrence or to death. We defined progression-free survival as the interval between the date of diagnosis and the date of tumour recurrence or the date of death, whichever occurred first.

Women with no recurrence were censored at their last follow-up date. We defined recurrence as a clinical examination or radiologic study with evidence of recurrent disease, preferably with pathologic confirmation or an increase of CA 125 greater than or equal to twice the upper normal limit on two occasions at least 1 week apart. We defined overall survival as the time between diagnosis and death or the last follow-up date. The women still living at the last follow-up date, 1 January 2011, were censored.

We calculated the Kaplan-Meier estimates of progression-free and overall survival in the time groups. We also calculated the survival figures for those patients who were treated by a gynaecologist (i.e., underwent a debulking surgery) because this group may primarily benefit from the collaboration. The log-rank test determined differences in Kaplan-Meier estimates.

Univariable proportional hazards models helped us study the influence of clinicopathologic factors on overall survival. We used a multivariable model to determine the effect of the study period on survival adjusted for other prognostic variables. All *P* values are two-sided, and we considered the associations significant at $P<.05$. We used the Statistical Package for Social Sciences version 16.0 for the analyses.

RESULTS

A total of 1,554 patients in the region had epithelial ovarian cancer diagnosed. Table 1 shows their clinicopathologic characteristics. Most of these patients had advanced stage of disease. No International Federation of Gynecology and Obstetrics stage was recorded in the medical records for 107 patients, and the pathology reports or surgical reports (or both) did not clarify the exact stage. Three of the patients were categorised as having early stage disease diagnosed and 98 patients had advanced stage disease diagnosed. The stage remained unclear for six patients who were excluded from the analysis of surgical outcomes.

Table 1 shows the characteristics during the various study periods. During the last period, more serous cancers and fewer adenocarcinomas "not otherwise specified" were diagnosed. The grade was more often unknown in this last period. Patients more often received adequate platinum-based chemotherapy over time ($P=.04$).

Only patients who needed staging surgery were included in the staging analysis. Staging was not applicable for 1,033 patients because an advanced stage became clear before or during surgery. A total of 362 patients underwent primary staging surgery, and another 91 patients underwent staging surgery secondarily, for example, when initially benign or borderline disease had been expected. The information was lacking for one patient.

The reasons for omitting a staging procedure were recorded in 68 medical records. The main reasons were fertility, another indication for chemotherapy (tumour histology), and poor condition. The proportions of omitted staging surgeries for the three calendar periods were somewhat similar: 15 (3.4%) for the first period; 29 (5.1%) for the second period; and 24 (4.4%) for the third period. A gynaecologic oncologist more frequently performed the surgery for patients with an RMI more than 200. Gynaecologic oncologists were involved in 33.9% of the surgeries during the first period, in 57.5% during the second period, and in 87.5% during the third period. Table 2 shows that gynaecologic oncologists performed increasingly more adequate staging procedures and surgeries during the 14-year study period.

Table 1. Characteristics of the study population.

Characteristic	Total (N=1,554)	Surgical study groups				Survival study groups		
		1996-1999 (*n*=440)	2000-2004 (*n*=568)	2005-2009 (*n*=546)	*P*	1996-2000 (*n*=550)	2001-2004 (*n*=560)	*P*
Age at diagnosis (y)	64 (17-95)	63.2 (20-95)	63.1 (18-91)	63.9(17-92)	.95	63.1 (20-95)	62.7 (18-91)	.63
Stage*					.22			.95
Early	351 (22.6)	103 (23.4)	138 (24.3)	110 (20.1)		133 (24.2)	136 (24.3)	
Advanced	1,197 (77.0)	337 (76.6)	425 (74.8)	435 (79.7)		415 (75.4)	421 (75.2)	
Unknown	6 (0.4)	0	5 (0.9)	1 (0.2)		2 (0.4)	3 (0.5)	
Histology					<.01			<.01
Serous	645 (41.5)	142 (32.3)	236 (41.5)	267 (48.9)		182 (33.1)	242 (43.2)	
Mucinous	120 (7.7)	36 (8.2)	42 (7.4)	42 (7.7)		44 (8.0)	45 (8.0)	
Endometrioid	208 (13.4)	72 (16.4)	81 (14.3)	55 (10.1)		90 (16.4)	77 (13.8)	
Clear cell	82 (5.3)	25 (5.7)	28 (4.9)	29 (5.3)		33 (6.0)	22 (3.9)	
Adenocarcinoma NOS	312 (20.1)	127 (28.9)	108 (19.0)	77 (14.1)		142 (25.8)	110 (19.6)	
Other	81 (5.2)	20 (4.4)	31 (5.5)	30 (5.5)		29 (5.3)	38 (5.0)	
Unknown	106 (6.8)	18 (4.1)	42 (7.4)	46 (8.4)		30 (5.4)	36 (6.5)	
Grade					<.01			.03
I	172 (11.1)	59 (13.4)	67 (11.8)	46 (8.4)		73 (13.4)	63 (11.3)	
II	315 (20.3)	112 (25.5)	112 (19.7)	91 (16.7)		135 (24.5)	104 (18.5)	
III	665 (42.8)	180 (40.9)	255 (44.9)	230 (42.1)		223 (40.5)	258 (46.1)	
Unknown	402 (25.9)	89 (20.2)	134 (23.6)	179 (32.8)		121 (21.6)	135 (24.1)	

Characteristic	Total (N=1,554)	Surgical study groups				Survival study groups		
		1996-1999 (*n*=440)	2000-2004 (*n*=568)	2005-2009 (*n*=546)	*P*	1996-2000 (*n*=550)	2001-2004 (*n*=560)	*P*
Karnofsky score†					.29			.30
Less than 40	19 (1.2)	4 (0.9)	9 (1.6)	6 (1.1)		5 (1.0)	11 (1.9)	
40-60	244 (15.7)	84 (19.1)	95 (16.8)	65 (11.9)		106 (19.3)	89 (15.9)	
More than 60	1,131 (72.8)	333 (75.7)	440 (77.4)	158 (65.6)		448 (74.8)	441 (78.7)	
Unknown	160 (10.3)	19 (4.3)	24 (4.2)	117 (21.4)		27 (4.9)	19 (3.5)	
Risk of malignancy index					.97			.83
Median	2,466 (57.9)	2,376 (52.3)	2,506 (16.1)	2,452 (59.2)		2,394 (81.9)	2,524 (87.1)	
More than 200	900 (29.3)	230 (32.7)	347 (24.3)	323 (31.7)		450 (32.7)	488 (21.1)	
Unknown	455	144	138	173		180	118	
Chemotherapy‡					.04			.04
Yes	895 (57.6)	241 (54.6)	317 (55.8)	337 (61.8)		291 (52.9)	329 (58.8)	
No	659 (42.4)	200 (45.4)	251 (44.2)	208 (38.2)		259 (47.1)	231 (41.3)	

NOS, not otherwise specified.

Data are median (range) or *n* (%) unless otherwise specified.

* Early, International Federation of Gynecology and Obstetrics stages I and IIa; advanced, International Federation of Gynecology and Obstetrics stage IIb or higher.

† As described in Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, editor. Evaluation of chemotherapeutic agents. New York (NY): Columbia University Press; 1949. p 196.

‡ Defined as at least six adjuvant courses or at least three adjuvant courses after neoadjuvant courses of platinum-based chemotherapy.

A total of 1,197 patients had disease that was International Federation of Gynecology and Obstetrics stage IIb or more, as clinically or surgically determined. Of these patients, 737 (61.6%) underwent primary debulking surgery. Clinical data for three patients were lacking. In 457 women, the primary debulking surgery was cancelled. The decisions about debulking surgery were based on clinical signs, imaging studies, or the patient's refusal. The decision also could be made soon after the surgery started, after inspection of the tumour alone. The main reasons for omitting primary debulking were the clinical condition of the patient (n=126; 27.6%), tumour volume or localisation (n=232; 50.8%), patient refusal (n=43; 9.4%), or a combination of these reasons (n=26; 6.2%).

In the group of 457 patients for whom the primary debulking surgery was cancelled, 165 patients underwent interval debulking. The tumour volume or localisation was the main reason for notperforming the primary debulking. A total of 902 patients (75.3%) with advanced stage disease received a primary or interval debulking, and this proportion remained stable over the study period.

Table 2. Results of the staging procedures for patients with epithelial ovarian cancer (*n*=453).

Characteristic	1996–1999 (*n*=139)	2000–2004 (*n*=190)	2005–2009 (*n*=124)	*P**
Adequate procedure†	32 (23.0)	61 (32.1)	77 (62.1)	<.01
Staging procedures				
Abdominal hysterectomy	133 (95.6)	175 (92.1)	118 (95.2)	.36
Bilateral salpingo-oophorectomy	122 (87.7)	170 (89.4)	119 (96.0)	.63
Infracolic omentectomy	135 (87.8)	187 (98.4)	123 (99.2)	.11
1 peritoneal biopsy	87 (62.6)	122 (64.2)	101 (81.5)	<.01
1 lymph node	51 (36.7)	88 (46.3)	98 (79.0)	<.01
10 lymph nodes	45 (32.4)	66 (34.7)	59 (47.6)	<.01
Surgeon attending				
Gynaecologic oncologist	51 (36.7)	104 (54.7)	100 (80.6)	<.01

Data are *n* (%) unless otherwise specified.

* χ^2 test.

† Adequate procedure defined as including omentectomy, bilateral salpingo-oophorectomy, at least one biopsy, and one lymph node.

The proportion of primary debulking surgeries decreased and the proportion of interval debulking surgeries increased (Table 3). The proportions of optimal and complete debulking increased. The debulking surgeries were increasingly performed by a gynaecologic oncologist. The location of the interval debulking changed significantly over the years.

Figure 1 shows the Kaplan-Meier curves of the progression-free and overall survival in the patient groups with diagnoses before and after the collaboration. Survival was not significantly different during the two periods, and survival did not improve significantly for patients who underwent debulking surgery (Fig. 2). Table 4 shows the variables that independently influence overall survival. Younger age, early stage, endometrioid or mucinous histology, lower tumour grade, no residual tumour or residual tumour smaller than 1 cm, attendance of a gynaecologic oncologist, and adequate chemotherapy were associated with prolonged survival. The type of hospital was not associated with survival outcome. Using multivariable Cox regression, we determined the following six independent variables: age; stage; tumour grade; completeness of debulking; presence of a gynaecologic oncologist; and adequacy of chemotherapy.

Table 3. Debulking procedures for patients with advanced stage epithelial ovarian cancer.

Characteristic	1996–1999 (*n*=337)	2000–2004 (*n*=425)	2005–2009 (*n*=435)	*P**
Primary debulking	230 (68.2)	280 (65.9)	227 (52.2)	<.01
Cancelled primary debulking	93 (30.7)	138 (32.6)	198 (45.9)	<.01
Interval debulking	37 (11.0)	75 (17.6)	144 (33.1)	<.01
Patients undergoing primary or interval debulking	251 (74.5)	320 (75.3)	328 (75.4)	.62
Optimal (less than1 cm) debulking	143 (57.4)	215 (68.0)	244 (76.5)	<.01
Complete debulking	60 (24.1)	118 (37.3)	139 (43.4)	<.01
Gynaecologic oncologist at primary debulking	73/230 (31.7)	176/280 (62.9)	186/227 (81.9)	<.01
Gynaecologic oncologist at interval debulking	24/37 (64.9)	50/75 (66.7)	129/144 (86.9)	.001
Hospital of debulking				<.01
University	33 (9.8)	57 (13.4)	96 (22.1)	
Teaching	122 (36.1)	151 (35.5)	129 (29.7)	
Nonteaching	143 (42.3)	150 (41.9)	126 (29.0)	

Data are *n* (%) unless otherwise specified.

* χ^2 test.

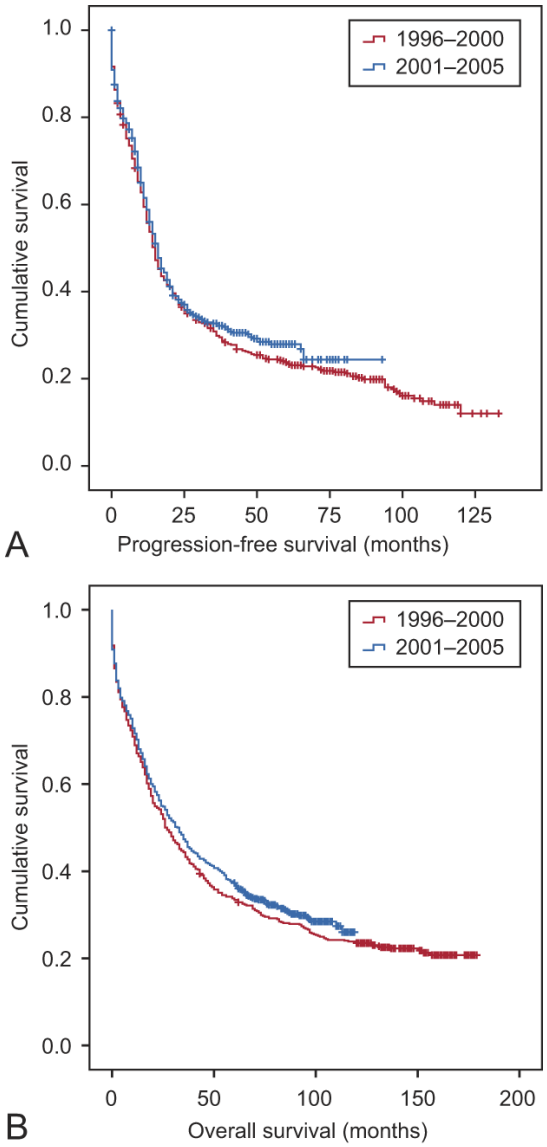

Figure 1. Kaplan-Meier estimates of progression-free survival (**A**) and overall survival (**B**) of all 550 patients with epithelial ovarian cancer diagnosed between 1996 and 2000 and of the 560 patients with epithelial ovarian cancer diagnosed between 2001 and 2005. Vertical bars indicate patients with censored data (alive at the last follow-up date). The log-rank test showed no significant difference in progression-free survival (*P*=.26) or in overall survival (*P*=.23).

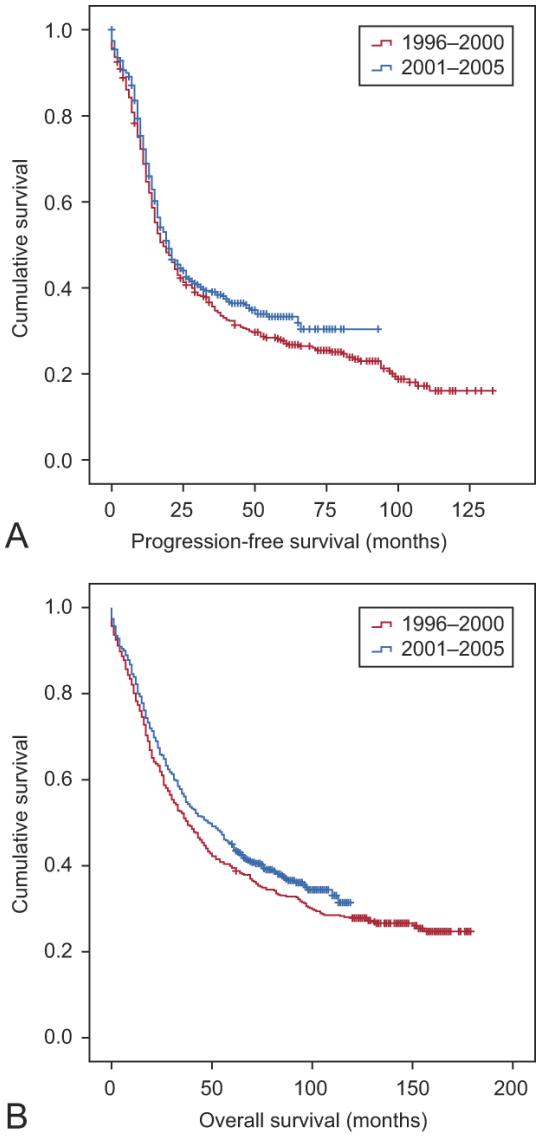

Figure 2. Kaplan-Meier estimates of progression-free survival (**A**) and overall survival (**B**) of 441 patients undergoing debulking surgery with epithelial ovarian cancer diagnosed between 1996 and 2000 and of 460 patients with epithelial ovarian cancer diagnosed between 2001 and 2005. Vertical bars indicate patients with censored data (alive at the last follow-up date). The log-rank test showed no significant difference in progression-free survival (*P*=.11) or in overall survival (*P*=.09).

Table 4. Overall survival by clinicopathologic variables of patients with epithelial ovarian cancer diagnosed between 1996 and 2005.

Clinical variable	Crude HR	95% CI	Adjusted HR	95% CI
Study period				
1996–2000	1.00	Reference	NA	
2001–2005	0.92	0.80-1.06		
FIGO stage				
I	1.00	Reference	1.00	
II	2.15	1.51-3.07	2.36	1.61–3.46
III	5.74	4.52-7.30	4.16	3.00–5.76
IV	8.60	6.32-11.69	5.71	3.76–8.66
Histology				
Serous	1.00	Reference	NA	
Mucinous	0.49	0.35-0.67		
Endometrioid	0.50	0.39-0.63		
Adenocarcinoma NOS	1.45	1.22-1.72		
Other	0.73	0.57-0.95		
Grade				
I	1.00	Reference	1.00	
II	2.73	1.98-3.76	1.94	1.35–2.79
III	3.74	2.76-5.05	1.90	1.34–2.70
Age (y)				
Younger than 40	1.00	Reference	1.00	
41–59	1.46	1.06-2.01	0.96	0.69–1.35
60–74	2.06	1.51-2.81	1.19	0.85–1.66
Older than 75	5.36	3.88-7.40	2.13	1.47–3.10
Optimal debulking				
Yes	1.00	Reference	NA	
No	3.29	2.70-4.01		
Complete debulking				
Yes	1.00	Reference	1.00	
No	3.39	2.84-4.04	1.60	1.26–2.04
Chemotherapy				
Yes	1.00	Reference	1.00	
No	1.56	1.36-1.79	1.81	1.44–2.28

Table 4. Continued

Clinical variable	Crude HR	95% CI	Adjusted HR	95% CI
Gynaecologic oncologist at debulking				
No	1.00	Reference	1.00	
Yes	0.81	0.69-0.94	0.78	0.66–0.93
Hospital volume				
Fewer than 20 surgeries per year	1.00	Reference	NA	
More than 20 surgeries per year	0.91	0.78-1.06		

HR, hazard ratio; CI, confidence interval; NA, not applicable; FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified.

DISCUSSION

This study describes all changes occurring after the regional collaboration for epithelial ovarian cancer started in the Netherlands. One prominent change was the increase in surgeries performed by gynaecologic oncologists. Introducing the RMI in risk assessment may have contributed to this change. Both the staging and debulking results improved greatly during the collaboration. Several care changes after the collaboration started may have improved the surgery. These changes include multidisciplinary consultation before treatment, using the RMI, having gynaecologic oncologists attend the surgeries, the organisation of care for the patients, and the protocols and guidelines that are being used in the network. Unfortunately, we cannot determine the precise reason for the improvements because of the retrospective design of the study.

Gynaecologic oncologists attended the staging surgeries of more than 85% of the patients with an RMI more than 200. Most of the remaining 15% were treated in one hospital where the semi-specialising gynaecologist operated with a specialising general surgeon. One might question the use of the RMI, which may increase the number of surgeries performed by gynaecologic oncologists for benign tumours. However, van den Akker et al.[12] show that the opposite is true. Moreover, a recent study shows that using the RMI to centralise care is cost-effective.[15]

While discussing the adequacy of the staging procedure, we found that more than 70% of the study population did not undergo optimal staging according to the definition of the Dutch evidence-based guideline for epithelial ovarian cancer, which includes at least 10 lymph nodes. The benefit of a staging procedure including 10 lymph nodes has never been proven with respect to survival, but we know that patients with early stage disease with a well-differentiated tumour can be spared chemotherapy.[16-18] The role of biopsies of normal peritoneum is still being debated.

We chose to present the procedures in the Dutch guideline, which are compatible with the quality indicators defined by the European Organisation for Research and Treatment of Cancer–Gynaecological Cancer Group.[19]

In a minority of cases, the surgeon outlined the reason for inadequate staging and the majority of reasons were valid. We advocate further research to identify factors that affect compliance with the guideline in daily practice.

In contrast to the circumstances of the staging procedure, the gynaecologists were aware of the inadequate procedure for debulking surgery. The reasons for not achieving complete debulking were recorded for most of the patients. Tumour volume and localisation were the main reasons; these are well-known factors negatively influencing debulking.[20,21]

The increase in interval debulking surgeries may have contributed to more complete debulking. Studies of interval debulking surgery and survival are contradictory[22,23] because of confounding by indication. We have no data regarding operative morbidity, which might have added interesting information about the differences between primary and interval debulking surgery.

Approximately 25% of all patients with advanced stage disease had no debulking surgery, and this proportion was stable over time. This is consistent with data for the whole Dutch population.[24] Apparently, a subgroup of patients is ineligible for surgery mainly because of the volume or localisation of the tumour or patient characteristics such as age and comorbidity.

Despite the improvement in clinical care, survival did not improve. There was a nonsignificant difference in overall 5-year survival of 3% (from 36% to 39%). An improvement of 3% overall survival would be compatible with the Dutch nationwide figures for survival,[24] in which 5-year relative survival has improved (35% in 1989–1993 compared with 41% in 2004–2009). The lack of a significant difference between groups could be attributable to inadequate study size. A post hoc power analysis determined that at least 3,045 patients per study group would be necessary to show a significant increase of 3% in 5-year survival, based on our observed survival.

The lack of an increase in survival also may be attributed to other factors like the inappropriate chemotherapy treatment. Chemotherapy was inadequate for approximately 30% of the patients. Chemotherapy was not started for 25% of these patients because of their poor clinical condition. The remaining patients, especially during the first study period, never received a platin-containing chemotherapeutic or they never received the adequate number of courses, mainly because of their condition.

Other factors are the increasing number of high-grade tumours in the second study period, and tumour grade is associated with survival in the Cox regression analysis. The increased percentage

of serous carcinomas and fewer adenocarcinomas not otherwise specified are probably caused by improved diagnostics and therefore are not considered a real shift.

This population-based study covered 14 years and all surgical aspects of ovarian cancer care, including reasons for omitting procedures. Although there is enough knowledge about adequate surgical procedures, many patients worldwide do not receive the best treatment, partly because of lack of collaboration between institutions and physicians. The results of this study look promising for future collaboration in the field of gynaecologic oncology. Regional networks can help in several ways to enhance management.

FINANCIAL DISCLOSURE

The authors did not report any potential conflicts of interest.

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General discussion

Several methods of preoperative evaluation of ovarian tumours have been reported in literature. These include imaging techniques such as transvaginal and transabdominal ultrasound, computed tomography (CT) scanning, magnetic resonance imaging (MRI), three-dimensional ultrasound, and colour Doppler. Furthermore, tumour markers such as cancer antigen 125 (CA 125) and human epididymis protein 4 (HE4), as well as proteomic techniques are studied. In addition, with advances in technology over the years, genetic materials are investigated for their use as tumour markers. Epigenetic mechanisms including DNA methylation are extensively studied[1,2] and could be useful in diagnosing ovarian cancer.

On the basis of several of these techniques, at least 20 prediction models for the ovarian cancer risk estimation have been developed and externally validated. The Risk of Malignancy Index (RMI)[3] was the first prediction model suitable for use in clinical practice. Four versions of the RMI have been developed and the first three versions were validated retrospectively and prospectively in a variety of clinical studies.

Preoperative assessment is of interest to patient counselling, as well as to the choice of the optimal surgical route, but it often requires intraoperative confirmation in order to prevent inadequate surgical management (under- and overtreatment). Frozen section analysis is generally accepted as a reliable intraoperative diagnostic tool, and is widely used in the intraoperative evaluation of ovarian tumours.[4-6]

The studies in this thesis focused on the RMI, frozen section analysis, and standardised laparoscopic examination as preoperative and intraoperative diagnostic tools to discriminate between benign ovarian tumours, borderline ovarian tumours (ovarian cancers of low malignant potential), and ovarian cancer.

ULTRASOUND MODELS IN THE PREOPERATIVE EVALUATION OF OVARIAN TUMOURS

Subjective impression of an experienced ultrasound examiner is currently believed to be the best approach to assess an ovarian tumour and no other method or model has proved superior.[7] Several papers have been published addressing the reproducibility of gynaecological ultrasound. Basically they all reached the same conclusion: subjective examiner impression is reproducible among expert examiners but not among nonexpert examiners or trainees.[8,9] The term 'expert examiner' was variously described as: gynaecologist or radiologist with expertise in gynaecological ultrasound and a special interest in adnexal pathology;[7] examiner who had more than 10 years of experience in gynaecological ultrasound;[10,11] examiner with more than 15 years of experience;[8] senior clinician who had performed at least 5,000 ultrasound scans;[9] and examiner who had performed over 10,000 gynaecological ultrasound examinations.[12]

Most women do not have (easy) access to expert ultrasonographers yet. Prediction models may help less experienced ultrasonographers. The RMI is a popular tool because of its simplicity: little experience in ultrasound diagnosis is required to identify the ultrasound features that have to be scored (namely: presence of multilocular lesions, solid areas, bilaterality, ascites, and intra-abdominal metastases), and the algorithm can be calculated easily. The study described in Chapter 2 validated the RMI and found sensitivity and specificity levels above 80% for discrimination between benign and malignant ovarian tumours with a cut-off level of 200.

Several other diagnostic models have been developed since the introduction of the RMI, and some perform better.[13] Recent studies suggested the International Ovarian Tumour Analysis (IOTA) Simple Rules (SR)[14] as the approach of choice when expert ultrasound expertise is not available. The SR are easy to apply, but are applicable (i.e. give a conclusive result) in only 77% of ovarian tumours[15] and do not provide risk estimates. In case the SR are inconclusive, expert ultrasound assessment is indicated.

The Logistic Regression model LR2 from IOTA is useful to skilled ultrasonographers only, as the model requires strict compliance with the ultrasound techniques, terms, and definitions set out by the IOTA team.[16] Both the SR and LR2 were published after the introduction of our study protocol on the external validation of the RMI and were therefore not included in this thesis. They are very promising, yet more difficult in their use. These IOTA models should be included in any future evaluation of ovarian tumour prediction models.

The IOTA models have not yet been implemented in the Netherlands. Currently, a prospective multicenter Dutch cohort study is being conducted on the performance and cost-effectiveness of the SR, followed by subjective assessment or MRI when needed, compared to the RMI (SUBSONiC-study).[17] The results of this study have to be awaited, but they may have major consequences for current Dutch guidelines for women with adnexal masses.

The recently developed Assessment of Different NEoplasias in the adneXa (ADNEX) model[18], also by IOTA, seems a promising new triage tool for women with ovarian masses. It is the first predictive multiclass model able to differentiate between four subgroups of malignant tumours (borderline, early stage, advanced stage, and metastatic ovarian cancer). The area under the receiver operating characteristic curve (AUC) for the discrimination between benign and malignant tumours was 0.94 (95% confidence interval 0.93 to 0.95) on temporal validation. The AUC was 0.85 for benign versus borderline, 0.92 for benign versus FIGO stage I cancer, 0.99 for benign versus FIGO stage II-IV cancer, and 0.95 for benign versus secondary metastatic cancer, respectively. AUCs between malignant subtypes varied between 0.71 and 0.95.

Future studies should focus on external evaluation of the ADNEX model to make sure it performs well in various populations, and eventually to evaluate whether incorporating the new model in clinical practice actually improves outcomes for women.

TUMOUR SIZE AND THE EVALUATION OF OVARIAN TUMOURS

The RMI-4,[19] validated in a study described in Chapter 3, includes the variable 'tumour size'. Although tumour size is recognised as an independent predictor of malignancy, the additional effect on overall model performance may be small, or insignificant. This is illustrated by the LR2 model, which is a simpler alternative to the LR1.[20] The LR1 was the first logistic regression model the IOTA group developed, and included tumour size (maximum diameter of three measurements of the largest diameters of the lesion in two perpendicular planes) as an independent predictor. The LR2 omitted tumour size, and demonstrated similar performance on external validation.

Tumour size plays a role in the accuracy of frozen section analysis: in adnexal masses larger than 10 cm, a benign result of the frozen section diagnosis is less reliable compared to paraffin section evaluation.[21] This is caused by the nature of the procedure: there is inadequate time to take many slices during frozen section procedure and large tumours may require multiple slices. In paraffin section evaluation, the need for multiple slices of large tumours is clearly acknowledged, as it is advised by the Dutch national guideline for epithelial ovarian carcinoma to take at least one slice per cm diameter, in respect of the diversity of histological components that ovarian tumours may contain.[22]

MENOPAUSAL STATUS AND THE EVALUATION OF OVARIAN TUMOURS

The risk of ovarian cancer is significantly higher in postmenopausal than in premenopausal women. The first publication on the RMI[3] identified postmenopausal status as an independent risk factor for malignancy, and included it as a parameter in the index.

Neither the LR1 and LR2, nor the ADNEX model, included menopausal status but only used age. LR1 and LR2 included age, as stepwise multivariate regression analysis revealed age as an independent risk factor for the presence of malignancy (a 3.3% increase of odds for malignancy with each additional year of age).

In our study cohort, sensitivity and positive predictive value of the RMI (at a cut-off level of 200) were lower in premenopausal women (55% and 29%, respectively) than in postmenopausal women (90% and 56%, respectively). Based on our results described in Chapter 5, we suggest an RMI cut-off of 100 in postmenopausal women to indicate frozen section analysis, whereas a cut-off of 200 is advised in premenopausal women. This implicates that postmenopausal women with an RMI score over 100 should be referred to centre hospitals with the proper expertise available to perform a staging procedure if necessary after frozen section analysis. Further prospective

research is recommended to determine whether the RMI cut-off level of 100 is to be implemented in the clinical management of postmenopausal women with ovarian tumours.

LAPAROSCOPIC EVALUATION OF OVARIAN TUMOURS

Over the last decades, the use of laparoscopy in adnexal mass surgery has increased. One concern, however, is the possibility of encountering an unsuspected ovarian malignancy at the time of surgery, given that there is no way to preoperatively identify malignant adnexal masses with 100% sensitivity and specificity. Laparoscopic surgery is associated with a higher risk of intraoperative cyst rupture, which upstages an unexpected ovarian cancer to International Federation of Gynecology and Obstetrics (FIGO) stage IC, with the consequences of possible need for adjuvant chemotherapy, and a worse prognosis. Furthermore, there is a risk of port-site metastases after laparoscopic procedures, although some authors state that this is a surrogate for advanced disease and should not be used as an argument against laparoscopic surgery.[23,24]

The potential adverse events of laparoscopic surgery in ovarian malignancies appear to be rare, and Muzii et al.[25] estimated (based on pooled data from laparoscopic case series in literature) a rate of unexpected ovarian cancer of 1% in the general population of patients with ovarian cysts and masses approached by laparoscopy. In postmenopausal patients the rate of (unexpected) ovarian cancer rises to 3%. In masses that demonstrate suspicious features during preoperative ultrasound, the rate of ovarian cancer rises further to 13%. This illustrates the need for careful patient selection: postmenopausal patients whose preoperative ultrasounds show suspicious features may not be the most suitable candidates for laparoscopic removal of an ovarian mass.

It has not been determined whether a standardised laparoscopic examination of an ovarian tumour contributes to diagnosing the tumour type, compared with the surgeon's overall impression based on physical examination, preoperative imaging modalities, and tumour markers. Implementation of a standardised system may improve the quality level of laparoscopic examination of ovarian tumours, and ultimately may decrease the risk of spilling the contents of a malignant mass. Our study in Chapter 6 showed only fair to moderate agreement on the diagnosis of malignancy. Overall sensitivity of diagnosis of malignancy was 49% in observers deprived of clinical information, with a specificity of 95%. Once clinical information was provided the sensitivity and specificity were 61% and 94%, respectively.

Presence of adhesions seemed to be an independent predictor of ovarian cancer in Chapter 4, but although the interobserver agreement for presence of adhesions was good (κ=0.71) for observers deprived of clinical information, adhesions were not only observed in malignant cases (38%) but also in benign cases (44%), endometriosis in particular. Once clinical information was provided, interobserver agreement for presence of adhesions was moderate (κ=0.52), and adhesions were

observed in 27% of malignant and 40% of benign cases. Our results of laparoscopic assessment of ovarian tumours may be brought on by the study method: the use of video recordings may not reflect conditions during standard laparoscopic examination by the observers, resulting in inaccuracies in the assessment of diagnostic features. Furthermore, in our study the number of malignant and borderline cases was too low with respect to benign cases.

Future studies on laparoscopic observation of ovarian tumours need to focus on live laparoscopic images including consecutive patients for a representative sample of study patients.

ALLOCATION OF BORDERLINE TUMOURS IN STUDIES INVOLVING OVARIAN TUMOURS

To allocate borderline tumours to either benign or malignant is debatable in any study involving ovarian tumours. We allocated borderline tumours to the benign group in Chapters 2, 3, 4 and 5 because the primary goal for developing the RMI was the distinction between malignant and borderline and benign cysts. The objective was the referral of patients with ovarian cancer to gynaecologic oncologists for appropriate surgical staging and possible tumour debulking surgery. The value of staging in borderline tumours is debatable, and it is generally accepted that omitting a staging procedure in such cases is unlikely to have a significant adverse effect on subsequent clinical management or prognosis.[26,27] In case borderline tumours were allocated to the malignant group, the test characteristics of the RMI would have changed, most importantly the sensitivity would lower from 81% to 62%.

When evaluating ovarian tumours intraoperatively (Chapter 6), we decided to group the borderline tumours with malignant tumours, given the high conversion rate from borderline to malignant on the final histology report.[28] In case borderline tumours were allocated to the benign group, overall sensitivity of diagnosis of malignancy in observers deprived of clinical information would rise from 49% to 70%; in observers provided with clinical information the sensitivity would rise from 61% to 77%.

CENTRALISATION OF CARE FOR OVARIAN CANCER PATIENTS

The treatment of ovarian cancer is now formally centralised in the Netherlands and only three of the 11 hospitals included in our studies still perform ovarian cancer surgery. The operations on patients with suspicion of malignancy are always performed by gynaecologic oncologists (centre hospital) or attended by gynaecologic oncologists (teaching hospitals).

CONCLUSIONS AND IMPLICATIONS

An accurate preoperative evaluation is essential to make sure that ovarian cancer patients are treated in high-volume institutions to ensure the best prognosis and survival chances. Prior knowledge of the nature of an ovarian mass is not only essential to the patient but also to the clinic in organising planning, costs, and overall management. Subjective impression by an experienced ultrasound examiner seems the best approach. When expert ultrasonographers are not available, the RMI can be used to predict the risk of malignancy. An RMI cut-off value of 200 is advised in premenopausal women to indicate frozen section analysis, whereas a cut-off of 100 is suggested in postmenopausal women. In the likelihood of a (borderline) ovarian malignancy, patients should be treated in centres with access to frozen section analysis and gynaecologic oncologists. The treatment of ovarian cancer is now formally centralised in the Netherlands.

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Summary | Samenvatting

SUMMARY

This thesis contains studies that evaluate opportunities to improve the preoperative and intraoperative diagnosis of ovarian tumours. As described in **Chapter 1**, the discriminative preoperative evaluation of ovarian tumours is rather difficult, as most ovarian masses are not immediately classifiable. The presumed diagnosis based on preoperative evaluation will guide the decision-making on the surgical approach. Treatment of benign ovarian tumours differs greatly from treatment of malignant tumours and the prognosis of women with ovarian cancer is influenced by appropriate surgery by a gynaecologic oncologist. An accurate preoperative diagnosis in women with ovarian tumours is therefore essential, not only to the patient but also to the clinic in organising planning, costs, and overall management.

Several diagnostic procedures are available for the assessment of ovarian tumours, and various prediction models for ovarian cancer risk estimation have been developed over time. The Risk of Malignancy Index (RMI) was the first diagnostic model for ovarian cancer risk estimation suitable for use in clinical practice. Four versions of the RMI have been developed and the first three versions were validated retrospectively and prospectively in a variety of clinical studies. **Chapter 2** describes a study that evaluated the RMI-3. We performed a prospective observational multicentre study in the eastern part of the Netherlands that included 548 women with ovarian tumours. All the patients included were preoperatively evaluated without applying the RMI. The RMI was calculated afterwards by using registered data, to hypothesise how the management would have been changed (regarding referral of patients to gynaecologic oncologists in specialised centres) if the RMI was used to discriminate patients with low and high risk for malignancy. The results showed an increase of ovarian cancer patients operated by gynaecologic oncologists from 64% in current practice to 80% if the RMI would have been applied with the cut-off level of 200.

Adding tumour size as an additional parameter to the model does not improve the performance of the RMI, as shown in **Chapter 3.** Our study validated the RMI-4 by applying the index to a new study population and comparing its performance with the RMI-3. The models demonstrated similar performances. We found lower sensitivity and specificity levels compared to the original report on RMI-4. This is a common finding of external validation of proposed models and illustrates the need for external validation of any prediction model before introducing into clinical practice.

Preoperative assessment is of interest to patient counselling, as well as to the choice of the optimal surgical route, but it often requires intraoperative confirmation in order to prevent inadequate surgical management (under- and overtreatment). Frozen section analysis is widely used in the intraoperative evaluation of ovarian tumours and is generally accepted as a reliable method. Various factors influence the surgeon's use of frozen section analysis, depending on the suspicion of malignancy. The study described in **Chapter 4** investigated factors relating to the use of frozen section analysis in ovarian tumours. We conducted a retrospective cohort study and included 670 patients who underwent surgery for an ovarian tumour. We concluded that frozen

section analysis is useful when the serum tumour marker cancer antigen 125 (CA 125) levels are greater than 35 units/mL and when there are multilocular tumours and solid areas visible on ultrasonography, and adhesions revealed during surgery.

Our study described in **Chapter 5**, evaluated the use of the RMI to indicate frozen section analysis in women with ovarian tumours. We concluded that women with an RMI below 20 do not need frozen section analysis, as their risk of malignancy is very low. Furthermore, we suggested an RMI cut-off of 100 in postmenopausal women to indicate frozen section analysis, whereas a cut-off of 200 is advised in premenopausal women. This implicates that postmenopausal women with an RMI score of over 100 should be referred to centre hospitals with the proper expertise available to perform a staging procedure if necessary after frozen section analysis.

Laparoscopy is a common approach as a diagnostic tool and for the surgical removal of (presumably benign) ovarian tumours. It has not been determined whether a standardised laparoscopic examination of an ovarian tumour contributes to diagnosing the tumour type, compared with the surgeon's overall impression based on physical examination, preoperative imaging modalities, and tumour markers. As a first step to investigate this subject, our study in **Chapter 6** evaluated diagnostic performances of evaluations of 41 videotaped laparoscopic examinations of ovarian tumours. The study showed only fair to moderate agreement on the diagnosis of malignancy. Overall sensitivity of diagnosis of malignancy was 49% in observers deprived of clinical information, and 61% in observers provided with clinical information.

Chapter 7 describes a retrospective population-based study on 1554 ovarian cancer patients in the eastern part of the Netherlands. This chapter gives an overview of all the changes that took place after starting a regional collaboration among ovarian cancer patients. The most prominent changes were that more surgeries were performed by gynaecologic oncologists. The regional introduction of the use of the RMI in risk assessment may have contributed to this change. Both the staging and debulking surgery results have greatly improved with the collaboration. A trend towards an improvement in survival could be seen over the period from 1996 till 2005.

In **Chapter 8** we discuss the outcomes of the studies described in this thesis. Subjective impression by an experienced ultrasound examiner seems to be the best approach to assess an ovarian tumour. When expert ultrasonographers are not available, the RMI can be used to predict the risk of malignancy. In the likelihood of a (borderline) ovarian malignancy, patients should be treated in centres with access to frozen section analysis and gynaecologic oncologists. The treatment of ovarian cancer is now formally centralised in the Netherlands.

SAMENVATTING

Dit proefschrift bevat studies naar het verbeteren van de pre-operatieve en intra-operatieve diagnostiek van eierstoktumoren. Zoals beschreven in **Hoofdstuk 1** komen eierstoktumoren veelvuldig voor in de dagelijkse gynaecologische praktijk. Vaak is het lastig om pre-operatief een correct onderscheid te maken tussen een goedaardige eierstoktumor of eierstokkanker, omdat de meeste tumoren niet direct te classificeren zijn. Wanneer het vermoeden bestaat dat er sprake is van eierstokkanker, is verwijzing naar een oncologisch centrumziekenhuis noodzakelijk. Hier werken gynaecologisch oncologen die zijn gespecialiseerd in de vaak complexe operaties die nodig zijn om zoveel mogelijk tumorweefsel te verwijderen. Wetenschappelijk onderzoek heeft aangetoond dat wanneer de zorg voor patiënten met eierstokkanker wordt gecentraliseerd dit een gunstige uitwerking heeft op de lange termijn prognose en overlevingskans.

Er zijn verscheidene diagnostische middelen beschikbaar om eierstoktumoren te evalueren en in de loop der jaren zijn talrijke predictiemodellen ontwikkeld voor het voorspellen van de kans op kwaadaardigheid. De Risk of Malignancy Index (RMI) is het eerste predictiemodel dat geschikt was voor gebruik in de klinische praktijk. Er zijn vier versies van de RMI ontwikkeld en de eerste drie versies zijn veelvuldig onderzocht in diverse klinische studies. **Hoofdstuk 2** beschrijft een studie waarin we de RMI-3 evalueerden. We voerden een prospectieve observationele multicenterstudie uit in het oostelijk deel van Nederland en includeerden 548 vrouwen met eierstoktumoren. Alle geïncludeerde patiënten zijn pre-operatief onderzocht met de standaard diagnostische middelen, zónder het toepassen van de RMI. De RMI berekenden we achteraf zodat we konden beredeneren hoe de behandeling zou zijn geweest (wel of niet verwezen naar een gynaecologisch oncoloog) als de RMI zou zijn gebruikt om onderscheid te maken tussen patiënten met een lage en hoge kans op kwaadaardigheid. De resultaten van onze studie laten zien dat het percentage patiënten met eierstokkanker dat geopereerd zou worden door een gynaecologisch oncoloog zou stijgen van 64% in de huidige situatie naar 80% als de RMI zou zijn gebruikt (met een afkapwaarde van 200).

Het toevoegen van tumorgrootte als extra variabele leidt niet tot een verbeterde prestatie van de RMI, zoals **Hoofdstuk 3** laat zien. De studie die in dit hoofdstuk wordt beschreven, valideerde de RMI-4 door deze toe te passen op een nieuwe studiepopulatie en de testeigenschappen te vergelijken met de RMI-3. De modellen laten overeenkomstige resultaten zien. We vonden een lagere sensitiviteit en specificiteit dan in de originele rapportage over de RMI-4. Dit is een veel voorkomende bevinding van een externe validatie en geeft het belang aan van externe validatie van een predictiemodel voordat deze wordt toegepast in de klinische praktijk.

Pre-operatieve diagnostiek is van belang voor het adviseren van de patiënt en voor de keuze van de operatieve benadering. Vaak is intra-operatieve bevestiging nodig om een suboptimale operatieve behandeling te voorkomen (onder- en overbehandeling). Vriescoupe-diagnostiek is algemeen geaccepteerd als een betrouwbare intra-operatieve diagnostische methode en wordt

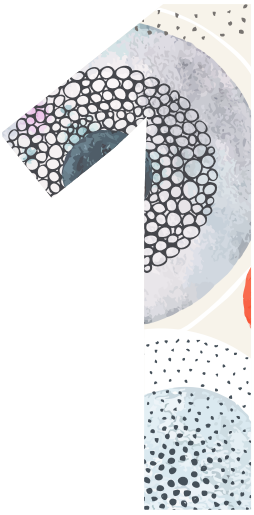
veelvuldig gebruikt in de intra-operatieve beoordeling van eierstoktumoren. Verschillende factoren hebben invloed op de beslissing van de operateur om vriescoupe-diagnostiek in te zetten, afhankelijk van de verdenking op kwaadaardigheid. De studie beschreven in **Hoofdstuk 4** onderzocht factoren die verband houden met de inzet van vriescoupe-diagnostiek bij eierstoktumoren. We voerden een retrospectieve cohortstudie uit en includeerden 670 patiënten die een ingreep ondergingen aan een eierstoktumor. We concludeerden dat vriescoupe-diagnostiek nuttig is bij een waarde van tumormerkstof CA 125 hoger dan 35 eenheden/ml, als er multiloculaire tumoren of solide partijen worden gezien bij echoscopisch onderzoek en indien verklevingen worden gezien tijdens de operatieve ingreep.

Onze studie beschreven in **Hoofdstuk 5** evalueerde het gebruik van de RMI in de beslissing om vriescoupe-diagnostiek te verrichten bij vrouwen met eierstoktumoren. We concludeerden dat bij vrouwen met een RMI lager dan 20 geen vriescoupe-diagnostiek nodig is, aangezien de kans op kwaadaardigheid in deze groep erg laag is. Verder suggereerden we een RMI-afkapwaarde van 100 in post-menopauzale vrouwen om vriescoupe-diagnostiek uit te voeren, terwijl een afkapwaarde van 200 van toepassing is bij pre-menopauzale vrouwen. Dit houdt in dat post-menopauzale vrouwen met een RMI van 100 of hoger verwezen zouden moeten worden naar een oncologisch centrum dat over de expertise beschikt om een stadiëringsprocedure uit te voeren.

Laparoscopie is een algemeen gebruikte techniek voor het operatief verwijderen van (vermoedelijk goedaardige) eierstoktumoren en dient tevens als diagnostisch middel om onnodige buikoperaties bij patiënten met goedaardige tumoren te voorkomen. Het is nog onduidelijk of een gestandaardiseerde laparoscopische benadering van een eierstoktumor bijdraagt aan het diagnosticeren van het tumortype, in vergelijking met de klinische inschatting van de chirurg gebaseerd op lichamelijk onderzoek, preoperatieve beeldvorming en tumormerkstoffen. Als eerste stap om dit te onderzoeken, evalueerde onze studie in **Hoofdstuk 6** de diagnostische waarde van evaluaties van 41 video-opnames van laparoscopische verrichtingen bij eierstoktumoren. De overeenkomst tussen de beoordelingen betreffende de diagnose van kwaadaardigheid was matig tot redelijk. De sensitiviteit van diagnose van een kwaadaardigheid was 49% bij beoordelaars geblindeerd voor klinische informatie en 61% bij beoordelaars die klinische informatie tot hun beschikking hadden.

Hoofdstuk 7 beschrijft een retrospectief population-based onderzoek bij 1554 patiënten met eierstokkanker in het oostelijk deel van Nederland. Dit hoofdstuk geeft een overzicht van alle veranderingen die plaatsvonden na de start van een regionale samenwerking rondom de zorg voor patiënten met eierstokkanker. De voornaamste verandering was dat meer operaties werden uitgevoerd door gynaecologisch oncologen. De regionale introductie van de RMI heeft hier mogelijk een rol bij gespeeld. Zowel de stadiëring als debulking operatie-uitkomsten zijn verbeterd door de samenwerking. Er is een trend te zien richting verbetering van de overleving tijdens de periode 1996 tot 2005.

In **Hoofdstuk 8** bespreken we de uitkomsten van de studies die in dit proefschrift staan beschreven. De subjectieve beoordeling door een ervaren echoscopist lijkt de beste manier om een eierstoktumor te evalueren. Indien ervaren echoscopisten niet beschikbaar zijn, kan de RMI worden toegepast om de kans op kwaadaardigheid te voorspellen. Indien er waarschijnlijk sprake is van een (borderline) kwaadaardigheid van de eierstok, zouden patiënten behandeld moeten worden in centra waar vriescoupe-diagnostiek en gynaecologisch oncologen beschikbaar zijn. De behandeling van eierstokkanker is in Nederland tegenwoordig formeel gecentraliseerd.



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CURRICULUM VITAE

Sabine van den Akker (15 augustus 1979) is geboren en getogen in het Brabantse Heesch. In 1997 behaalde ze haar VWO-diploma aan het Mondriaan College in Oss en startte met de studie Gezondheidswetenschappen aan de Universiteit Maastricht. In 2001 behaalde ze het doctoraaldiploma van de afstudeerrichting Biologische Gezondheidkunde. Haar eerste baan was die van onderzoeksmedewerker op de afdeling IQ healthcare van het Radboud universitair medisch centrum. In 2003 stapte ze over naar de afdeling Verloskunde & Gynaecologie en nam daar de coördinatie van twee internationale klinische interventiestudies op zich. In 2005 initieerde Sabine de PROBAAT studie (Protocollaire diagnostiek bij aanwezigheid adnextumor), het onderzoek dat onder begeleiding van Prof. Massuger, dr. Zusterzeel en dr. Kluivers heeft geleid tot dit proefschrift. Als datamanager speelt ze een belangrijke rol in het verzamelen en rapporteren van cijfers waarmee de kwaliteit van zorg inzichtelijk gemaakt wordt en verbeterd kan worden. Tevens is ze sinds 2011 actief betrokken bij het colposcopie-spreekuur. Sabine is lid van de Wetenschapscommissie van de afdeling Verloskunde & Gynaecologie. Ze instrueert junioronderzoekers en zorgt voor borging van de kwaliteit van het wetenschappelijk onderzoek. Sinds december 2015 is Sabine betrokken bij het Radboudumc Expertisecentrum voor Trofoblastziekten. Ze woont samen met Mark Flink in Nijmegen.

LIST OF PUBLICATIONS

van den Akker PAJ, Kluivers KB, Zusterzeel PLM, van Gorp T, Geomini PMAJ, Massuger LFAG. Prediction of ovarian histology by laparoscopic observation. Submitted.

van den Akker PAJ, Zusterzeel PLM, Aalders AL, Snijders MPLM, Samlal RAK, Vollebergh JHA, Kluivers KB, Massuger LFAG. Use of Risk of Malignancy Index to indicate frozen section analysis in the surgical care of women with ovarian tumors. Int J Gynecol Obstet 2016; in press.

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